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THE PROSTATE AT THE CROSSROAD*

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IN the light of recent developments in the field of obstructing lesions of the prostate (aside from acute pathology) it is interesting to note the numerous attempts that have been made to correct these conditions without resort to the now generally accepted method of enucleation by means of open operation.

Many years ago, Bottini, later followed by Chetwood, essayed the method of galvanocautery incision of the neck of the bladder, the approach to which in most instances was through a perineal exposure, with results so unsatisfactory that further efforts in this direction were practically abandoned.

Among the first really satisfactory methods of endo-urethral removal of bars or prostatic fibroses, was that of the punch apparatus of Young, which when limited strictly to these conditions and in the hands of experts, still functions as an effective procedure.

Later Caulk of St. Louis converted this instrument into a cautery punch and still later the writer of this paper had constructed a telescopic visualized punch with a pistol grip closure. A number of investigators produced other methods of this basic development by Young. Caulk with characteristic enthusiasm and rare courage, elevated the eyebrows of his more conservative colleagues, including the writer, with the statement that he was operating 80 per cent of his prostatic cases with the cautery punch. Incidentally he is substantiating his claim, not only through his own work but through that of others, notably Engel of Crile's Clinic, a brilliant young associate of Lower and a former pupil of the writer, who has performed with the Caulk method 30 odd operations during the past year with highly satisfactory immediate results.

In this country the first reported cases wherein prostatic encroachment on the urethra and vesical outlet treated endoscopically with the high frequency current were exhibited by the writer nineteen years ago before the Urological Section of the New York Academy of Medicine. One was a case of lobulated prostatic enlargement with 14 ounces of residual urine, in which the patient remained well with a perfectly functioning bladder during a period of ten years' observation. The second, a patient with median lobe hypertrophy, with 4 ounces residual urine, returned with the same symptoms, after a period of five years.

The outcome of subsequent attempts in the general application of this method were such as to lead to the conclusion that with the instrumental and electrical equipment of that day, it was not equal to the exacting demands of this highly technical procedure.

Stern of New York later developed what he called a resectoscope. He believed that in this instrument he had a revolutionary

* Read before the Bellevue Hospital Alumni Association, New York City, October 7, 1931.

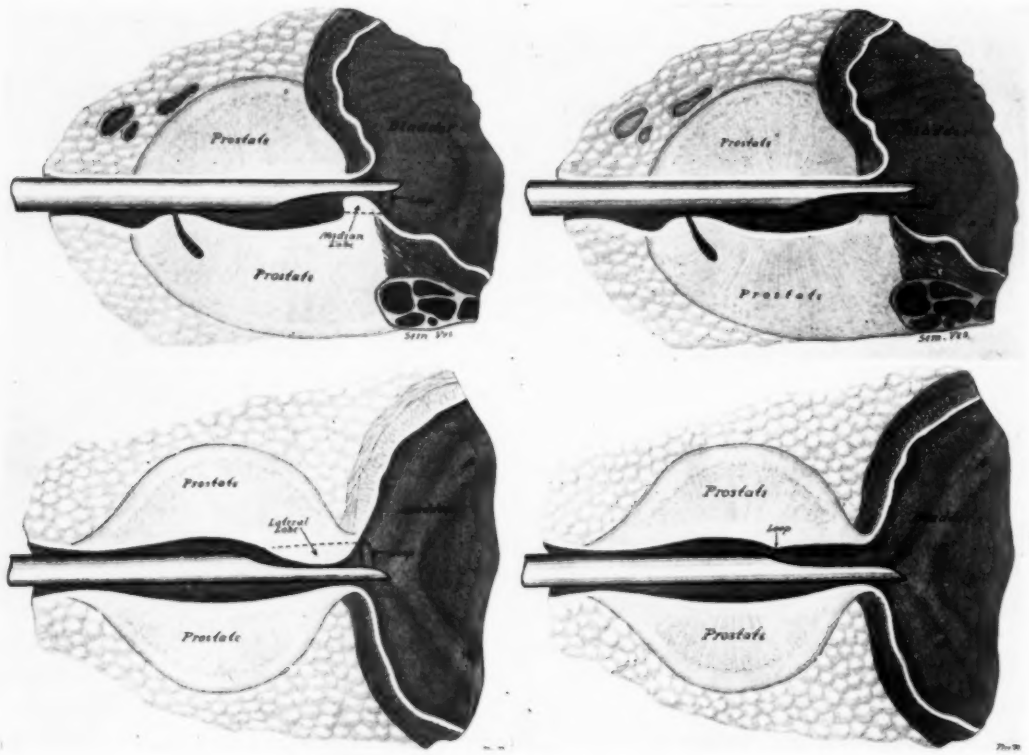
method for partial excision of the prostate, at least that portion of the gland that hindered the natural emptying of the bladder. If he did not accomplish quite that much, at least he had assembled the essential elements thereof. It is to be regretted that he did not carry the method through to its logical conclusion.

Devis of North Carolina, a painstaking student of the subject, took up this work and to his great credit has demonstrated that the removal of prostatic encroachments per urethra, by means of an electrical cutting current adapted to an urethroscope, is a wholly feasible operation.

Luys of Paris also has performed a somewhat similar operation which he calls "fourrage de la prostate."

Foley of St. Paul has demonstrated an ingenious method of instrumental endourethral prostatectomy.

Without in any way wishing to derogate from this constructive work, and with a deep sense of appreciation for its personal impress, it has seemed to this writer that these various methods, while highly constructive and in the hands of these men effective, leave much to be desired before a general application of endoscopic prostatic resection can come into universal use.



Figs. 1 to 4.

The ideal requirements for this operation are as follows:

1. The most precise visualization of the prostatic urethra.

2. The greatest possible flexibility of manipulation *under vision*, of the electric cutting loop.

3. Ample electrical power to excise the obstructing prostate under water with a coincidental minimum of hemorrhage and of *tissue coagulation*.

4. Interchangeability and ease of manipulation of electrodes, in the closure of bleeding points.

5. The completion of the operation including the introduction of a No. 24 French whistle tip indwelling catheter,

with but one introduction of the instrument, the sheath being withdrawn after the catheter has been passed through it.

This has been rendered possible by the remarkable achievement of Mr. Frederick Wappler of New York City, whose research

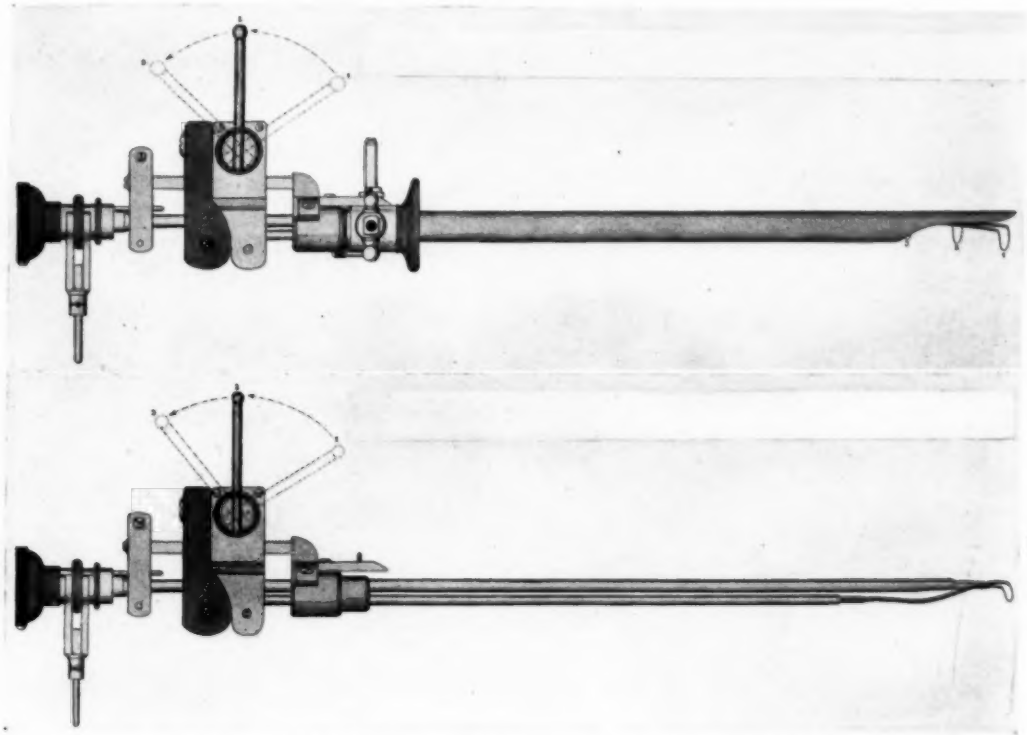


Fig. 5.

Fig. 6.

Fig. 5.—McCarthy visualized prostate electrode assembled.
Fig. 6.—Shows cutting and optical construction.

6. Rapid epithelialization with a minimum of cicatrization.

on this question (at the solicitation of the writer) has culminated in the construction

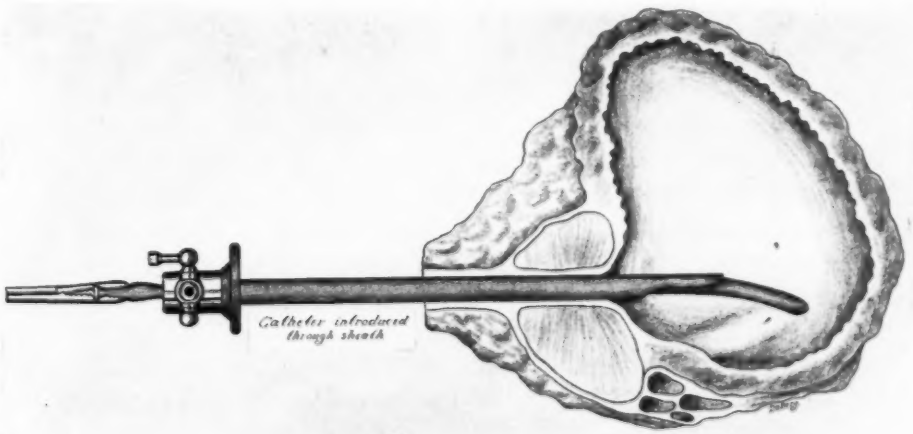


Fig. 7.

For the first time in medicine the equipment herewith described adequately meets these exacting demands.

of an electric arc cutting machine, that insofar as the writer is aware, has not been hitherto attainable. It supplies a degree

of cutting power and desirable current characteristics for the excision of tissue under water, or other aqueous media, greatly in excess of any possible clinical requirement.

The well-known pan-endoscopic system of vision of this author, with a non-conducting bakelite sheath together with the accompanying cutting loop electrodes, constitutes the armamentarium.

With this equipment in the hands of an experienced urologic clinician, who has been trained in the use of the pan-endoscope, wherever it is possible to introduce the instrument, it is demonstrably feasible adequately to treat all cases of prostatic fibrosis—the majority of cases of prostatic hypertrophies—to afford symptomatic relief in the presence of scirrhous types of carcinoma of the prostate, without resort to open operation. It may also serve in certain cases as an ideal measure in the early diagnosis of prostatic carcinoma.

A word of caution should be interjected here to admonish the casual instrumenteur, or the occasional surgeon, that this is not a simple procedure. It is in fact a highly technical one, to be essayed only by those expert with instruments and qualified to cope with the occasional difficulties that in a large series of cases are inevitable.

Nor should it be performed promiscuously, or under circumstances preventing personal supervision of the postoperative care. In fact the only mortality encountered by the writer since the inauguration of this study occurred under the latter conditions.

In the cases treated by this method to date, there has been a notable absence of worry on the part of the surgeon, patient and family, which have been an all too frequent concomitant of open prostatectomy. The brevity of hospital domicile, two to ten days, and in this respect we have perhaps

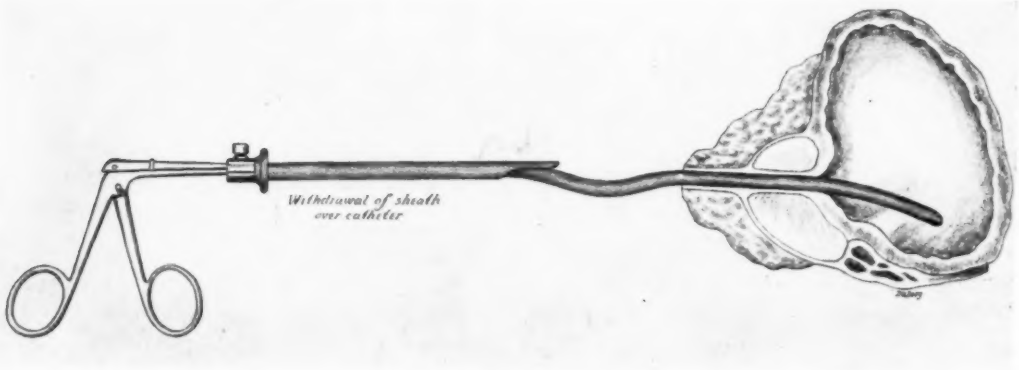


Fig. 8.

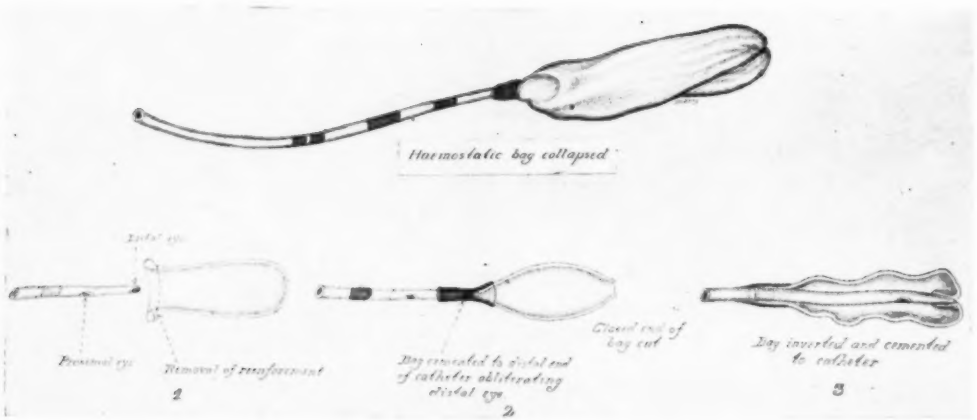


Fig. 9.

been ultraconservative, has, especially in these days, decided economic advantages.

Following the hospital domicile there is a brief period of increased frequency of micturition, which soon disappears. In but 2 of our cases was there any noticeable degree of post-hospital discomfort, which was in no measure comparable to the obvious and prolonged disability following open prostatectomy.

In this series we have treated types of prostatic obstruction from the *now* simple fibrosis, to the complete retention of middle and lateral lobe enlargement, with symptomatic relief and the ability completely to empty the bladder.

Now if these assertions be true, and we are prepared to substantiate them, the case types previously described should constitute but a minor field of application, for this advanced technique. If it is possible by this method, as is here asserted, to remould the prostatic urethra at will, to remove with complete facility early prostatic encroachments or fibroses, it would seem the method should experience its greatest usefulness in the first field of medicine, Prophylaxis.

CONCLUSION

It should be the duty of the internist and general practitioner to more closely scrutinize and evaluate the symptoms of individuals in the prostatic range, of nocturia, hesitancy at the onset, feeble and prolonged micturitional act, terminal dribbling, etc. In all cases residual urine should routinely be estimated.

For the very good reason that, if the judgment of the writer is not strabismic, it is quite within the domain of the probable to prevent these prostatic obstructive manifestations, with their attendant pathologic sequelae, their accompanying morbidity, mental and physical.

Obviously, the prostate in more senses than one, is "At the Crossroad."

Since the reading of the foregoing paper, much has been gained in the way of additional clinical experience, not only on the part of the writer and his immediate associates, but also with a number of collaborators throughout the country.

There have also been added to the technical equipment certain refinements,

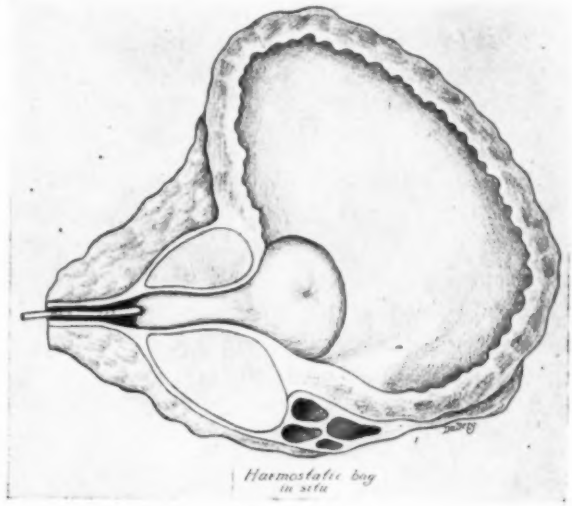


Fig. 10.

as well as preventive measures for the control of oozing in the unusual type of case. Pertinent questions have also been asked, which will be herein answered.

The acid test of time generally acts as a brake on early enthusiasm. Here it has had the opposite effect on my immediate associates, my collaborators and myself. This is proved by our joint experience in several hundred cases. It has been stated that if a departmental head can sell a new procedure to his immediate associates, he can with equanimity face the outside world. For it is they who "follow through" on his cases, have a precise knowledge of postoperative complications, and poor end results cannot be glossed over.

It is our general conviction that the procedure is a revolutionary one, which will find a large and important place in the prevention and management of benign prostatic disease, and in the alleviation of the malignant.

The following questions have been asked:

How may the occasional active oozing be controlled? Bleeding points are visualized and coagulated under vision. The return flow should be free from color on the completion of the operation. Should there be persistent oozing difficult to control and involving excessive coagulation which

is not to be practiced, a balloon bag has been provided, which can be made in the clinic. The bag consists of a very thin finger cot of good quality, attached to a calibrated whistle tip ureteral catheter. The open end of the cot is freed of its reinforcement and by means of rubber cement, fixed to the distal end of the catheter. This fixation includes the end of the catheter and the distal eye, leaving the proximal eye free. Fine black silk is wound about the cemented end of the cot. A small opening is then made in the closed end of the cot, which is then inverted over the catheter, about three-fourths as far as it will go. It is important that the bag should be relaxed and not on the stretch; else when filled, it will bend the filling catheter. The end of the cot is then cemented to the shaft of the catheter below the proximal eye, the cemented portion is then reinforced with a winding of black silk and rendered smooth with cement substance. Acknowledgment is here made to my associate Dr. Joseph A. Hyams, for the final consummation of this valuable addition to our armamentarium. Thus constructed the operator has a simple and effective means of control in a manner similar to the Ballenger or Hagner bag. When well lubricated with liquid albolin it may be introduced through the sheath, the latter withdrawn, the bag inflated with 40–50 c.c. of water and drawn gently and with moderate firmness, into the prostatic urethra, about one third the pressure employed with the ordinary prostatic bag being used.

The bag may be maintained in position for one or two hours, after which it is deflated and withdrawn, and a No. 24 French whistle tip catheter introduced for drainage. The bag may be reintroduced at will by first passing the pan-endoscope.

How much tissue can be removed? As much as desired. The prostatic urethra may be remoulded at will.

It is well for urologists, even the most competent, to at first confine their work to the floor of the prostatic urethra. They will be surprised at the functional results noted. This work has exploded the previous misconception of the important role played in urinary obstruction by the lateral lobes.

What about the permanency of the procedure? The experiences of Caulk and Davis, who have concentrated their efforts on this field along different technical lines for a much longer period than the writer, would seem to indicate its relative permanency. Cysto-endoscopic study of our earliest cases reveals plastic, smooth urethrae, and a maintenance of symptomatic relief.

The crux of the matter may be summed up in the statement that medical men who know most about it elect this procedure for themselves in preference to the more radical prostatectomy. Inasmuch as it is attended with minimal risk, with but brief hospitalization, a repetition of the revision should not militate against it.

What about repeats? In our Clinic at the Post-Graduate Hospital there have been, all told, about half a dozen. This may be explained on the technical ground that we proceeded most cautiously until there was sufficient clinical background, as a basis for the further extension of the step.

What preliminary preparation should these patients have? The same as for prostatectomy. Especial caution must here be exercised in the toilet of the bladder and sterilization of the urine.

What is the immediate postoperative care? Frequent irrigation with sterile, normal salt solution through the catheter and the *constant maintenance of drainage.* Otherwise one must intervene and correct the condition.

When should the indwelling catheter be withdrawn? After the drainage has been constantly clear for two days. Generally on the third or fourth day.

Finally, because of the unprecedented interest in this procedure there is already at hand a large and rapidly accumulating amount of clinical data. This justifies the claims made in this paper, and will, at an early date, serve to determine its limitations as well as its precise field of application.

EXPERIMENTAL PRODUCTION OF SEVERAL VARIETIES OF BONE SARCOMA BY INTRAMEDULLARY INJECTIONS OF THE VIRUS OF THE FILTERABLE FOWL ENDOTHELIOMA TUMOR*

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WITH FOREWORD BY

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FOREWORD

THE first transplantable chicken tumor was discovered by Fujinami of Japan in 1909, and was a spindle cell sarcoma. This tumor had many remarkable features. It survived the destructive action of sunlight, *x*-ray and radium, and when dried, withstood heat up to 75°C. for thirty minutes.

Peyton Rous in 1911 revealed the fact that there was a certain disease in fowls closely resembling malignant tumors in man, and that although he was unable to isolate the causative agent, he could reproduce this tumor at will in Plymouth Rock fowls by injections of a cell-free filtrate. This was regarded as a most important and highly significant discovery because of the probable or possible analogy between these sarcomas in chickens and human malignant tumors. Whether these fowl tumors were caused by an organism so small that it could readily pass through a porcelain filter, or whether they were due to a so-called filterable virus or chemical agent, was a question that remained unanswered. Regardless of which theory was accepted, the fact remained that it was possible to produce in chickens, by an extrinsic agent, tumors that were believed to be true sarcomas, and which developed metastases precisely like the metastases in human cancer, causing death the same way.

In July 1925, Gye brought out his noteworthy contribution to experimental work upon the Rous sarcoma agent, and for a time it seemed that a definite step forward had been made in the solution of the hitherto insoluble problem of the etiology of malignant tumors. Gye started out with the hypothesis that malignant tumors were due to one or more microorganisms or viruses, which produced a malignant tumor only when the soil was made favorable by the breaking-down of the natural resistance of the body cells by some specific factor, known or unknown. In his own words:

> These researches have led me to look upon cancer—using the term in its widest sense—as a specific disease caused by a virus (or group of viruses). Under experimental conditions the virus alone is ineffective; a second specific factor, obtained from tumour extracts, ruptures the cell defences and enables the virus to infect. Under natural conditions continued "irritation" of tissues sets up a state under which infection can occur.

Gye believed he had proved the truth of his theory by treating the Rous sarcoma agent with chloroform until it had apparently become inert and could no longer cause tumors to develop in Plymouth Rock fowl; then later, by adding some other substances of varied nature, he was able to produce tumors. He called this other material which reactivated the inert virus, a *specific factor*.

Unfortunately no one else was able to repeat Gye's experiments. The conclusion reached by most critics was, that the Rous sarcoma agent had not been entirely destroyed by the chloroform and that the subsequent production of tumors, after adding the so-called *specific factor*, was due

* Gibney Memorial Fellowship Thesis, Laboratory of the Hospital for Ruptured and Crippled, New York. Submitted for publication December 29, 1931.

to the still active Rous sarcoma virus itself.

The failure of Gye to establish the proof of his theory in no way weakened the broader theory which I have held for many years: that malignant tumors are due to an unknown microorganism or microorganisms, widely distributed, to which most individuals are exposed, and which require a favorable soil for development.

In a paper on "Some Clinical Evidence in Favor of the Extrinsic Origin of Cancer"[1] I stated:

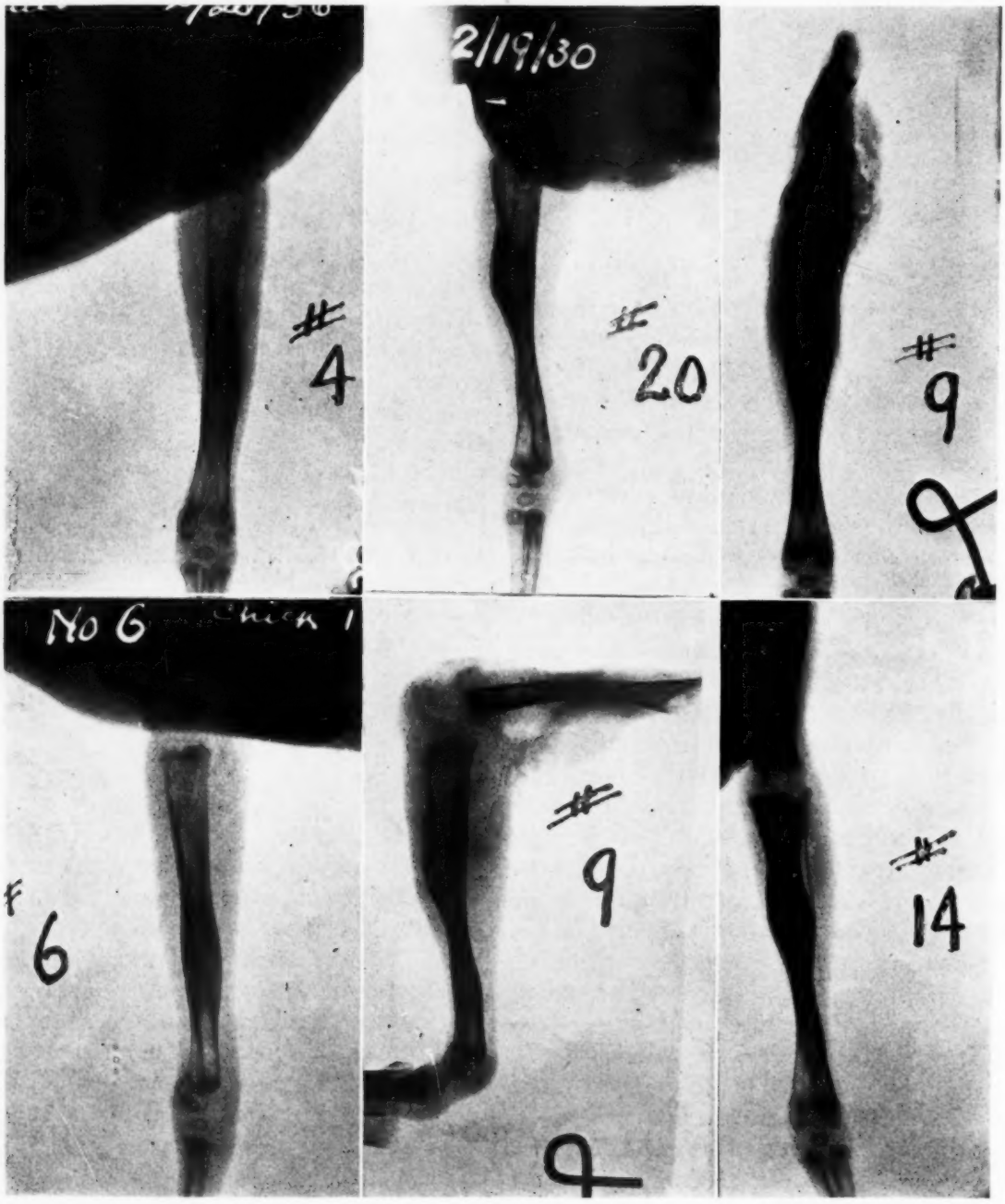

Fig. 1. Group 1. Typical *x*-ray appearance of bone involvement in this group. Chicks No. 4, 20, 9, 6, 14.

"If we assume the extrinsic cause of cancer, then it is easy to understand why the number of cancer cases varies in different geographical areas. It is easy to

[1] Read before The American College of Surgeons, October, 1924: *Surg. Gynec. Obst.*, 40: 353, 1925.

explain why some races have little or no cancer and others living in the same localities but with entirely different habits of living and diet have many cases of cancer. If we assume an extrinsic cause of the disease, it is easy to understand that this organism may be very widely distributed over the world, that everybody is exposed to it, and yet that it requires a soil peculiarly fitted for it to obtain a firm hold in man and produce a cancer. I do not believe that the question of *favorable soil* has ever received due recognition in discussions on the etiology of cancer. During the Great War, the Imperial Cancer Research Society of Great Britain had the members of its staff devote their entire time to the study of infections, abandoning for the time their research work in the field of cancer. A most important paper on "The Mechanism of Bacterial Infections, with Special Reference to Gas Gangrene" was brought out in the Sixth Scientific Report of the Imperial Cancer Research Fund, 1919, by two of these workers, Bullock and Cramer. In it they state that very many wounds, especially those received on the Western Front, were injected with the bacillus of Welch, but only a very small percentage of those infected wounds developed gas gangrene. The same thing was found to be true in

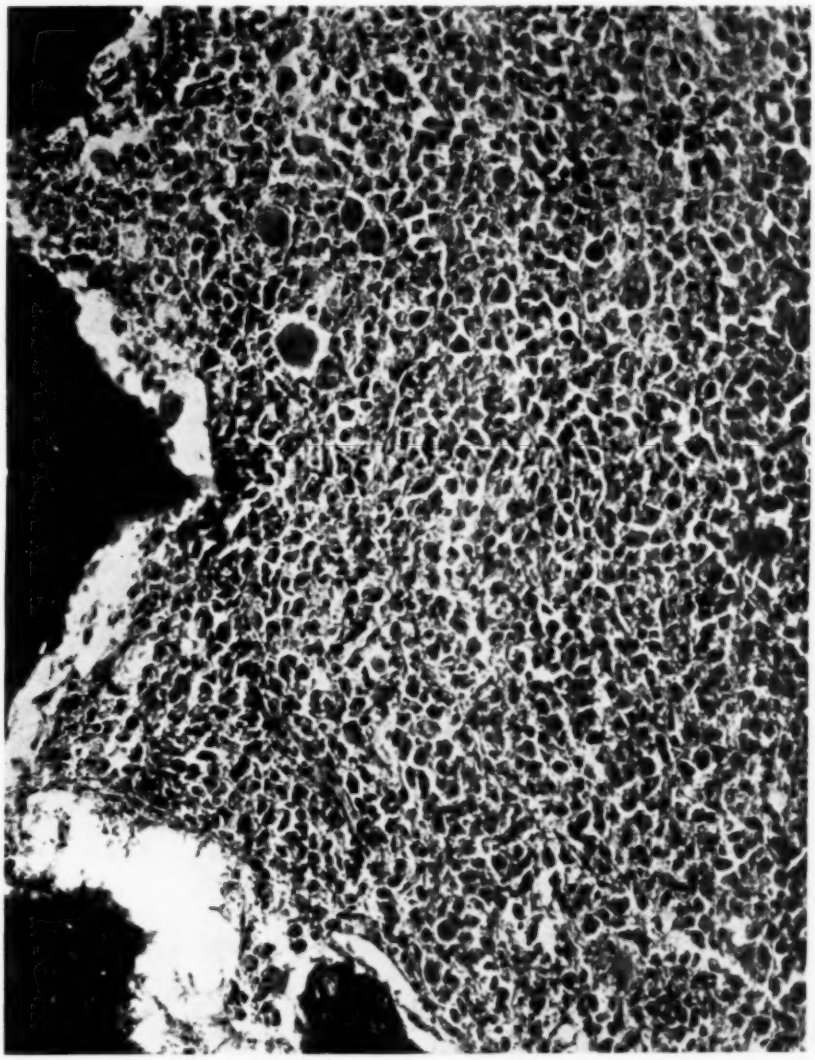

Fig. 2. Group 1. High power photomicrograph of bone tumor of group 1. Note cellular make-up of tumor, rounded or polyhedral cells, highly chromatic nuclei, and occasional giant cell. Chick No. 3.

animals; of some hundred mice and guinea-pigs injected with the bacteria of tetanus, only a very small percentage contracted

but rather that they effect a local breaking down of the defensive mechanism against the bacteria of gas gangrene and tetanus.

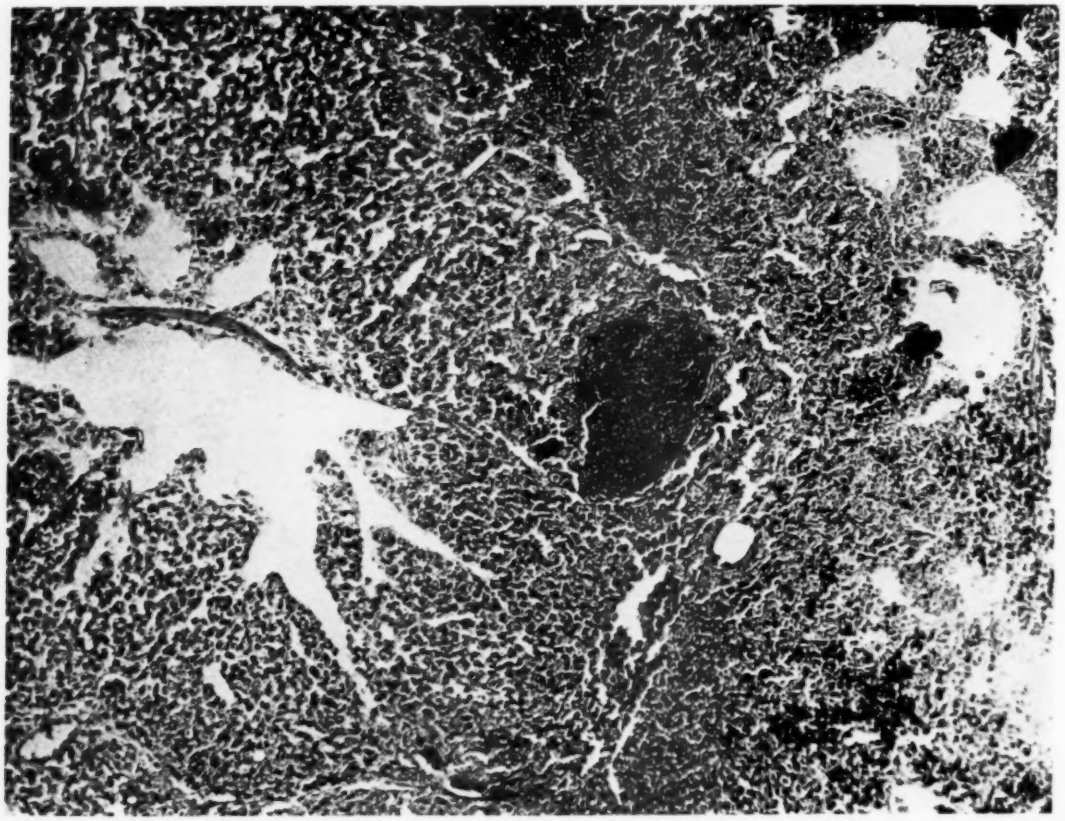

Fig. 3. Group 1. Tumor in lung associated with tumor in Figure 2. Note similarity of cellular elements. Chick No. 3.

the disease. It was found, however, that doses of 2.5 milligrams of calcium chloride, when injected subcutaneously into mice of 10–15 gram weight, together with a suspension of a virulent strain of bacillus welchii or *vibrion septique*, will produce a violent gas gangrene in every case. According to Bullock and Cramer: 'The normal animal disposes of the bacteria mainly by lysis and partly also by phagocytosis, and this defensive mechanism is so efficient as to render these bacteria non-pathogenic when injected by themselves. If a small dose of soluble ionisable calcium salt is injected together with the bacteria or their spores, the specific disease is elicited in a very virulent form.' In explaining this action, they do not believe that the calcium salts possess some power to increase the virulence of the organism; This new phenomenon they characterize as 'kataphylaxis.' These experiments, I believe, have a very important bearing on the question of cancer, and go far toward explaining how it might happen that a great many people—perhaps the majority—could be exposed to a micro-parasitic agent caused by cancer and only a very small percentage become infected."

In an editorial on the Ninth Scientific Report of the Imperial Cancer Research Fund[1] it is stated:

> The work of Gye was the first attempt to formulate a conception in which the development of malignancy in the filterable fowl tumors presented merely an exaggeration of the process underlying the development of malignancy in mammals. Although the experimental evidence he brought forward in support

[1] *Lancet*, Dec. 20, 1930.

of his views has not been accepted, his work has had the effect of establishing the fowl tumors as true malignant new growths.

Our investigations indicate very forcibly that we are confronted with a systemic infection characterized by long latency and exhibiting varied local manifestations, determined in type and site by the most diverse physical, chemical, mechanical, or animate irritants. Insidious invasion, long quiescence, complexity of secondary factors, muteness of symptoms, and protean nature of manifestations are the peculiar features which have baffled inquiry so persistently.

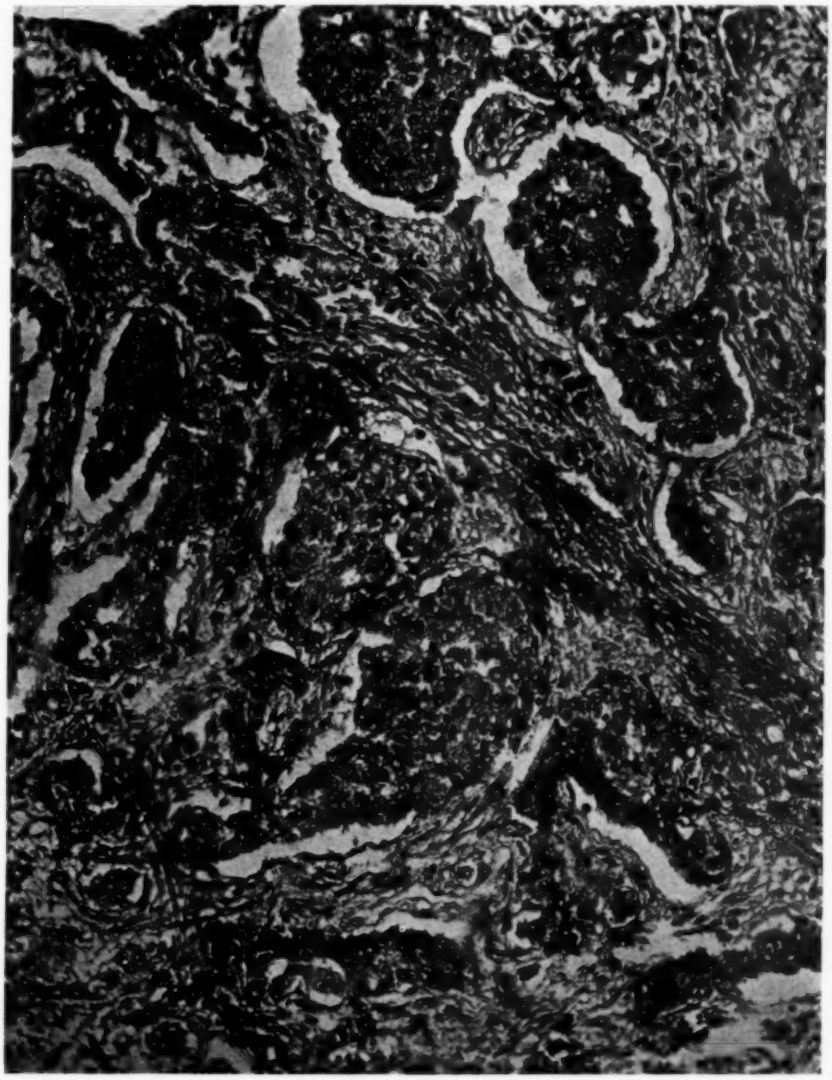

Fig. 4. Group 1. Tumor from nodules in liver of chick No. 9 of this group. Note epithelial structure of cellular element, for the most part in broad branching tufts.

The recent and very important survey of cancer in Westmorland County, England, of which a preliminary report was published[1] furnishes new evidence. This survey covered a period of two years, and was made by Dr. Louis Sambon, already widely known for his cancer investigations in various countries in Europe as well as in the American tropics. To quote it briefly:

The parasitic, unobtrusively infective nature of the disease is attested by its peculiar distribution both in time and place . . .

Perhaps the most striking, the most interesting discovery our investigations have elicited

[1] *Brit. M. J.*, 2: 1062, Dec. 7, 1929.

is the great prevalence of all types of malignant and other neoplasms in animals. We have met with cancer in all kinds of wild and domestic animals, in pet animals, and in animals used as food. We might mention horse, cow, sheep, hog, cat, dog, hedge-hog, rabbit, vole, mouse, fowl, turkey, goose, owl, canary and toad."

In a recent paper on "Cancer Control"[1] I have dealt more fully with the whole question of the extrinsic origin of malignant tumors in man.

[1] Coley, W. B. Cancer control. Am. J. Surg., 14: 605, Dec., 1931.

When Connor[1] published his experiments in the production of endothelioma in the tibia of young chickens, I became greatly interested and suggested to Dr. Richard F. Berg, who had just received the Gibney Memorial Fellowship at the Hospital for Ruptured and Crippled, and who had elected to spend his year in the study of bone sarcoma under my direction, that it might be worth while to repeat and try to carry along still further, the experiments of Connor. Through the kindness of Dr.

[1] Connor, C. L. Experimental sarcoma of bone. *Arch. Surg.*, 19: No. 5, Nov., 1929.

Fig. 5. Group 1. Silver stain preparation of same tumor as Figure 4. Note large amount of cellular, and small amount of fibrous elements.

W. E. Gye of London, I received some of the dried virus from the filterable fowl tumor (endothelioma) originally discovered in 1927 in the laboratory of Dr. Murray of the Imperial Cancer Research Fund, and with this, the following experiments were conducted. Berg not only confirmed Connor's experiment showing the possibility of producing typical endothelial myeloma or Ewing's sarcoma in the tibia of Rhode Island Red chicks, but, by using the tumors of the second and third series for inoculation, he was able to produce five different histological types of tumors closely simulating the different types of malignant bone tumors in man, four sarcomatous tumors, one epithelial tumor.

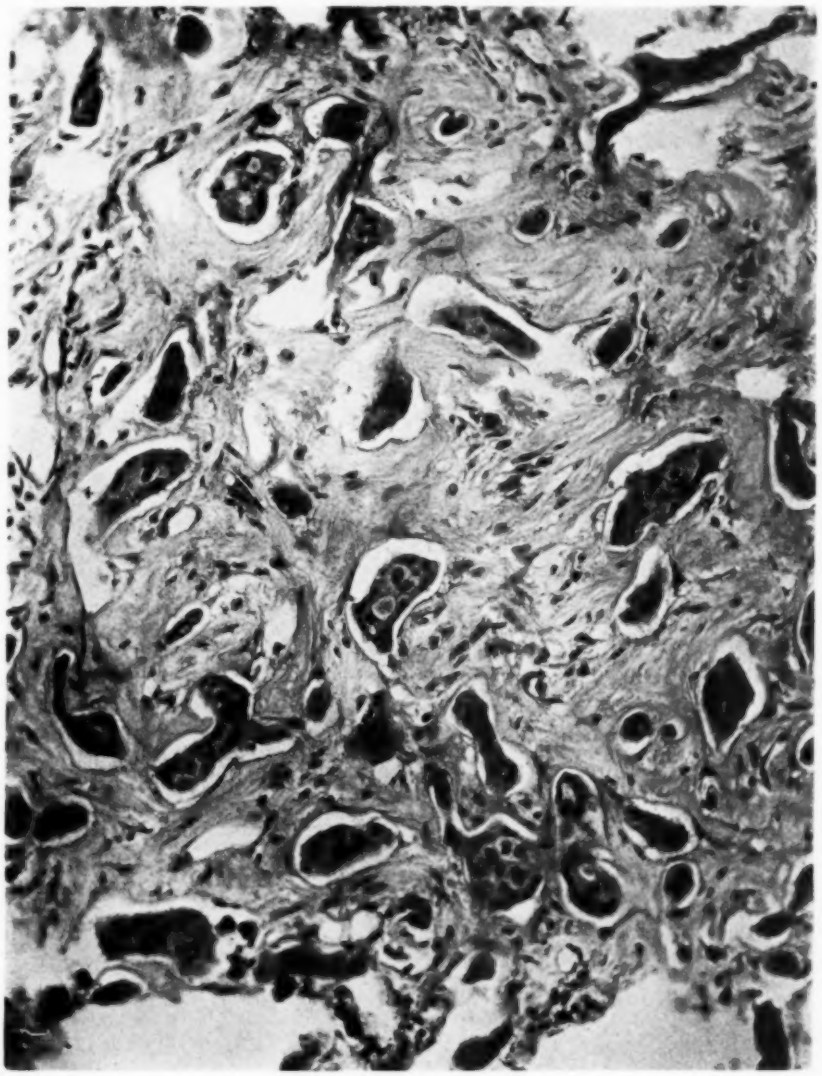

Fig. 6. Similarity of metastatic carcinoma in human (radius) to tumor seen in chick. Figure 4.

In this connection it is interesting to recall that Sir Charles Ballance of London at the meeting of the American Surgical Association just twenty-five years ago said that he not only firmly believed that malignant tumors were due to some form of microparasitic agent but he further believed that the same microorganism might, under different conditions, give rise to various histological types of tumors.

If there is an analogy between malignant tumors in animals and those in man, this experiment—the production of several different varieties of malignant tumors in animals—would show that it is not improbable that some similar extrinsic agent

might be able to produce the various types of malignant tumors in man. If there is no analogy between animal tumors and workers have continued to search for this living agent believing it to be the real cause of malignant tumors. Inasmuch as it was

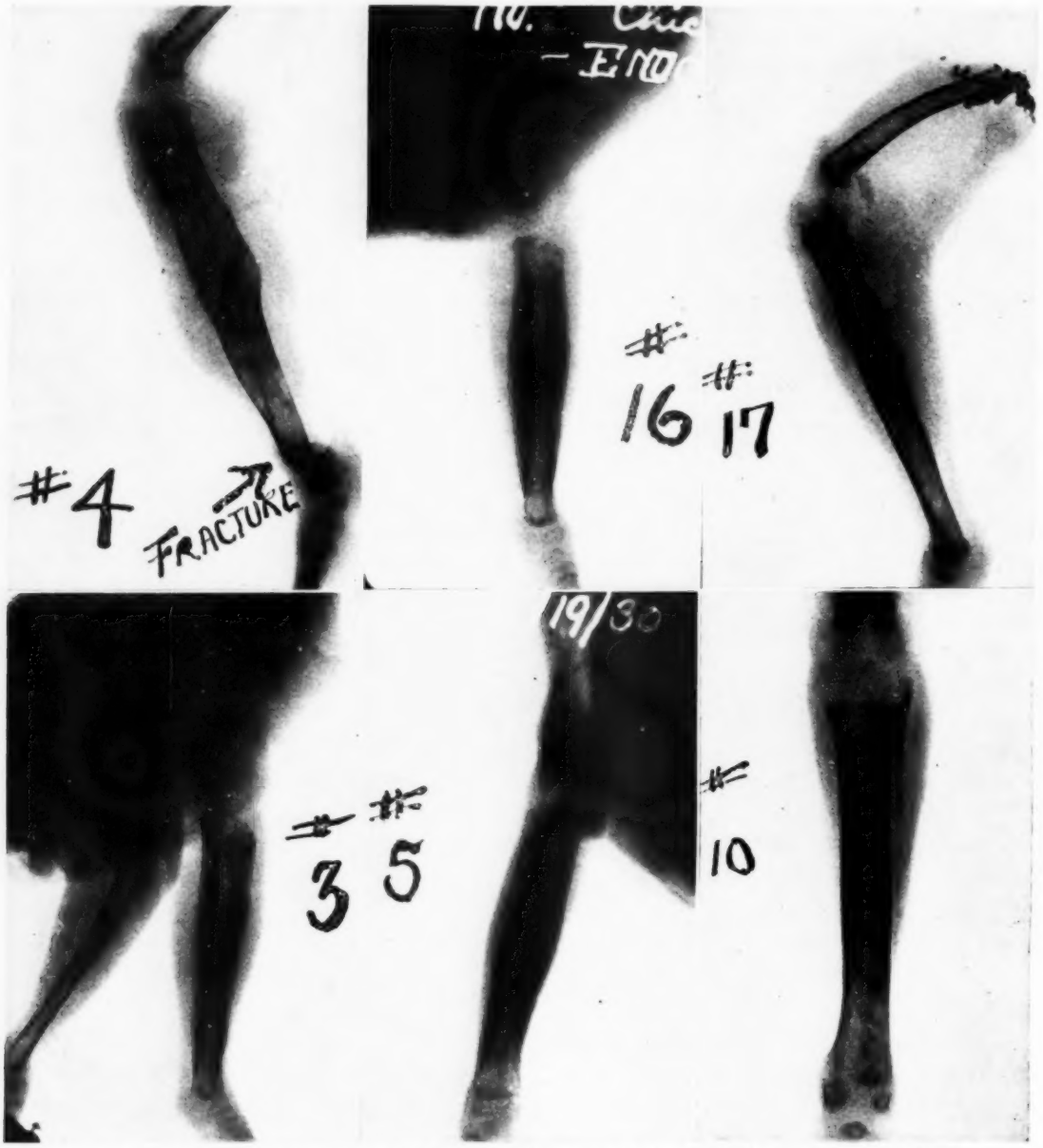

Fig. 7. Group 2. Typical *x*-ray appearance of bone involvement of the chicks in group 2. Chicks No. 4, 16, 3, 17, 5, 10.

human tumors then it would seem that a vast amount of money and labor on the part of research workers during the last thirty years has been spent in vain.

Although Rous, Gye, or other investigators have never been able to produce a pure culture or to isolate a living agent from the filterable fowl tumors, many found impossible to obtain a culture by the use of ordinary media, it occurred to me that it might be worth while trying the special medium prepared by Glover,[1] upon which, alone, he has been able to grow his own organism obtained from

[1] Glover, T. J. The bacteriology of cancer. *Canada Lancet & Practitioner*, 74: No. 3, 1930.

human cancer. Glover very kindly furnished us with some of his medium. After the first inoculation we obtained an organism in pure culture from the tumors Berg had produced.

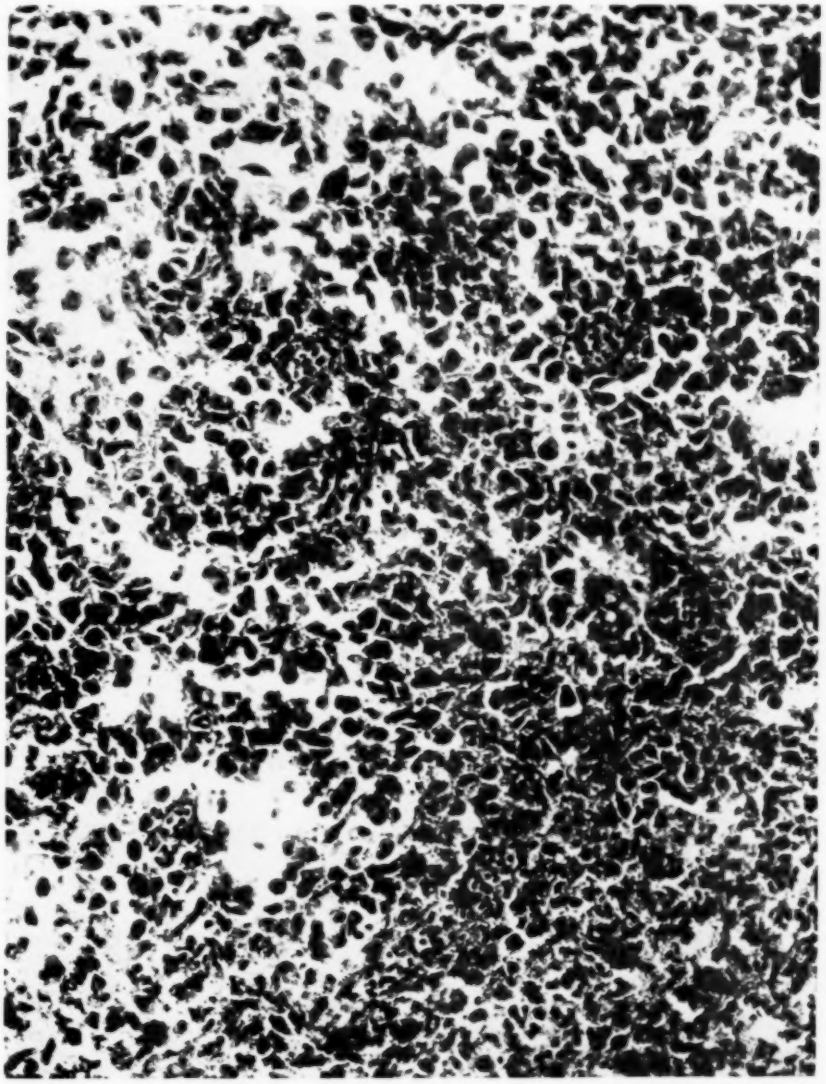

Fig. 8. Group 2. High power photomicrograph of typical tumor in group 2. Note similarity to that seen in typical tumor of group 1. Cells are for the most part of the endothelial type. Chick No. 4.

These tumors have been pronounced true malignant tumors by a number of experienced pathologists. We have compared the organism with the one found by Glover in human cancer, and believe it to be practically identical. Like Glover's, it is a pleomorphic organism, passing through the same stages of cyclic development, and, like the Glover organism, has a filterable stage. Likewise, with the filtrate, it is possible to produce tumors in animals.

During the last year (1931) experiments with this living organism have been carried on by Dr. John E. Sullivan (Dr. Berg's successor to the Gibney Memorial Fellowship of the Hospital for Ruptured and Crippled) and myself.[1] We have been

[1] Owing to a lack of facilities at the Hospital for Ruptured and Crippled for animal experimentation on a large scale, our later experiments with the organism were for the most part carried out at the Murdock Research Laboratory, Bronx, New York. We are greatly indebted to Dr. Thomas J. Glover, the Director of the laboratory, for his generous help and cooperation, without which the work would not have been possible.

able to produce tumors in chickens, pigeons, rats, rabbits and guinea pigs, by inoculations of pure cultures of this organism. These tumors have the characteristic clinical features of malignant neoplasms in man, and their histological structure is likewise characteristic. Furthermore they have been pronounced true malignant tumors by a number of experienced pathologists. A further report of the work will be published in the near future.

THE EXPERIMENTAL PRODUCTION OF SEVERAL DIFFERENT VARIETIES OF BONE SARCOMA

Richard H. Berg

PROTOCOL

The chickens used in this work were incubator hatched Rhode Island Reds, varying in age from one to seven days at the time of inoculation. Chicks were all from the same strain and same hatchery. For the first experiment the material furnished through the kindness of Dr. W. E. Gye was prepared according to his directions. Thirty chicks were used in this group. The dose was 0.2 c.c. of the filtrate injected into the pectoral muscles on one side. For some reason, none of these chicks developed tumors, so accordingly another series of 25 chicks were inoculated with 0.5 c.c. of filtrate prepared from the remaining portion of the dried tumor tissue. The material had evidently lost its power to produce tumors or there must have been a flaw in the technique for none of the second series developed tumors either. A second vial of dried tumor tissue was then obtained from Dr. Gye and this proved to be very active, and the results of the three following groups are described below:

Group 1.

Preparation of Filtrate. The technique used in all the experiments was as follows. Four grams of the dried tumor tissue together with a small amount of sterile silver sand were thoroughly mixed with distilled water by slowly adding the fluid until 100 c.c. had been used. This mixture was then transferred to centrifuge tubes and after a few minutes at slow speed the supernatant fluid was withdrawn and passed through a sterile Berkfeld candle; the resultant clear fluid was tested for its sterility. For convenience the fluid was transferred to 10 c.c. sterile vaccine ampules and sealed, ready for use.

Technique. Twenty-five chicks were inoculated, with careful asepsis, in two sites: 0.5 c.c. of the filtrate into the pectoral muscles and 0.2 c.c. into the medullary cavity of the tibia on the same side. This was done by forcing a needle through the knee joint downward into the medullary cavity.

Of this group:

21 chicks developed tumors in the breast
19 chicks in the tibia and breast
2 chicks in the breast alone
4 chicks with no tumors at all.

Most of the chicks died in from two to three weeks and the rest were killed and necropsies performed. The majority showed metastatic nodules in the lungs, liver and heart muscles, and one of the chicks of this group, No. 9, showed extremely numerous nodules in the liver which on pathological examination were considered to be of epithelial nature rather than connective tissue. Figures 4 and 5 show sections of this tumor. The bone lesions in this chick corresponded histologically to the others seen in the group (endothelial type). See Figure 1. This is a very interesting finding not easily explained and whether the tumors arose spontaneously and independently of the bone tumor in the tibia is a matter of conjecture. If it did arise as the result of the original injection, we would have to explain it on a transmutation basis. If we accept the latter explanation we must almost agree that the one causative agent in tumors is capable of producing a multiplicity of lesions, depend-

FIG. 9. Group 2. Section of bone tumor in chick No. 17, with compact arrangement of cells in marrow cavity, and lacunae. Bone shows destruction.

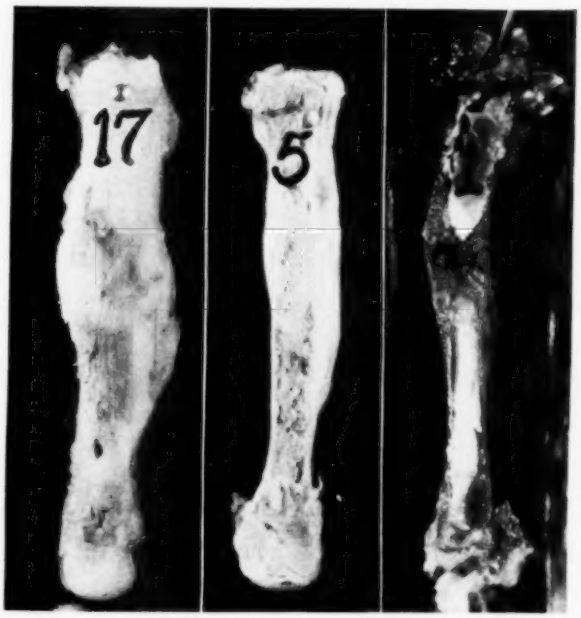

FIG. 10. Group 2. Gross specimen from bone tumor in chick No. 17. Note the marked bone destruction.

FIG. 11. Group 2. *x*-ray of tumor, with radiating spicules of new bone, and soft tissue involvement. A spontaneous tumor was also present in this chick in tarsal bone of same leg. Chick No. 6.

ing upon the site attacked. The other bone tumors were essentially similar from *x*-ray, gross and histological examination. Figure 2 shows a characteristic microscopic view of the tumors developed in this group. It is also similar to the tumor seen in chick No. 9 which developed the strange liver nodules.

Fig. 12. Group 2. Low power photomicrograph showing the radiating spicules of new bone and the thin remnants of the cortex in the center. Chick No. 6.

Group 2.

Twenty-five chicks were inoculated in this group with the filtrate obtained from the dried tumor tissue obtained from the breast tumors of group one. Chicks of this group were of the same strain as used in the first group, and were one week old. The same technique was used in preparing the filtrate as in the first group.

The tibias only were injected in this group, as we were particularly interested in bone lesions, breast inoculation being used primarily to replenish the stock of tumor tissue. The four chicks not developing any tumor in the first group were inoculated at the same time. All the chicks received 0.2 c.c. of the filtrate into the medullary cavity of the upper end of the tibia.

Of this group:
19 chicks developed bone tumor
6 chicks did not show any lesion.

Fig. 13. Group 2. High power photomicrograph of tumor seen in Figure 12, showing short spindle cells and new bone production. Spontaneous tumor arising in tarsus was almost identical to this. Chick No. 6.

Two rather interesting phenomena were noted in this group. In the *first place* the four older chicks from group one died within a few hours after the injection. The first one died within an hour and the last one died during the night. On necropsy there were no demonstrable gross lesions anywhere, and the conclusion was that it was an *anaphylactic* reaction for none of the other chicks died until tumors had developed. *Another* chick, No. 6, developed a rapidly growing tumor which was in most respects unlike the typical tumors produced in the group. This tumor resembled the true osteogenic type seen in man and further description of gross and pathological findings will be found under Figures 11, 12, and 13 and in the pathological descriptions following.

It is interesting to note that in this same chick a tumor identical to that arising at the site of inoculation developed in the tarsal bone of the same leg. This is rather interesting because it was either spontaneous or metastatic which is not often seen in this type of sarcoma. Necropsies were performed on the other chicks of this group

and practically all showed metastatic nodules in the lungs and to a less extent in the liver. The tumors were classified as

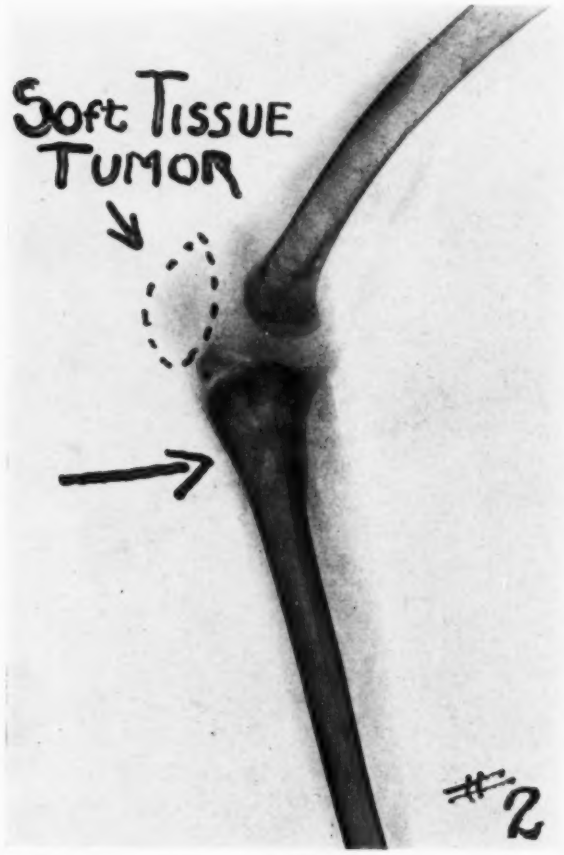

Fig. 14. Group 3. *x*-ray of chick No. 2, with soft tissue tumor anterior to knee and bone involvement at upper end of tibia.

endotheliomas and ran true to the characteristic form described in the first group. Figures 7 and 8 show such tumors.

Group 3.

Six chicks were used in this group due to the fact that it was impossible to obtain the required number at the particular time. These chicks were six weeks of age. The freshly prepared tumor solution filtrate obtained from chick No. 6, group 2 (osteogenic sarcoma) was prepared in the same manner as for groups 1 and 2. Due to the fact that the chicks were larger than those used in the other group, 0.4 c.c. of the filtrate was injected into the upper end of the tibia and 1 c.c. of the filtrate into the pectoral muscles of the same side. The chicks progressed in the usual manner.

Of this group: 5 chicks developed tumor in tibia and breast. 1 chick developed no tumor.

The first chick, No. 2, died on the twenty-third day. On necropsy, an unusual type of growth was noted about the knee joint and seemed to be entirely free from the bone tumor. It lay in the fascial space anterior to the articulation. It was incapsulated and appeared to be connected to the spot on the joint cartilage where the needle had been introduced into the medullary cavity. The bone was also involved in the process but did not show a remarkable swelling. The breast tumor was the size of a small hen's egg. Figure 14 shows the soft tissue tumor in bone involvement. Pathological description of the tumor is found under Figure 15. This tumor proved to be of the giant cell type. No gross lesions were noted in the liver or lungs. Another chick of this group was also of importance in regard to the production of a different type of tumor. This chick No. 3 died on the twenty-fifth day after inoculation, and showed a well-marked bone tumor, associated with a large breast tumor and considerable soft tissue involvement about the upper end of the tibia. From *x*-ray it appeared more like the myeloma type seen in humans. There were no demonstrable gross lesions in the liver or lungs (Fig. 18). Pathological description of the tumor apparently placed it in the classification of endothelial myeloma (Fig. 19). The other four chicks died within a few days of each other and all had well-developed breast tumors and bone tumors which resembled those of group 1 and 2, being of the endothelioma type. Small nodules were noted in the lungs of three of these chicks; no liver lesions were noted. The interesting feature of this group was the production of the different types of tumor tissue, the first being the giant cell, the second being the endothelial myeloma type, and the third the endothelioma type.

It would be very interesting to carry on this work on a much larger scale trying to pick out the unusual types of tumor from each group and transplanting them with the idea of developing other unusual types. All these chicks received the same care and type of filtrate, and it seems from the results obtained that the positive agent is very likely a filterable virus which is capable of producing various local tissue reactions. It might be interesting to experiment further on these lines by the addition of bacterial toxins or chemical agents, to determine if still other bizarre reactions might occur.

PATHOLOGICAL DESCRIPTION

Group 1.

Figure 1 shows the various types as seen by *x*-ray in group 1.

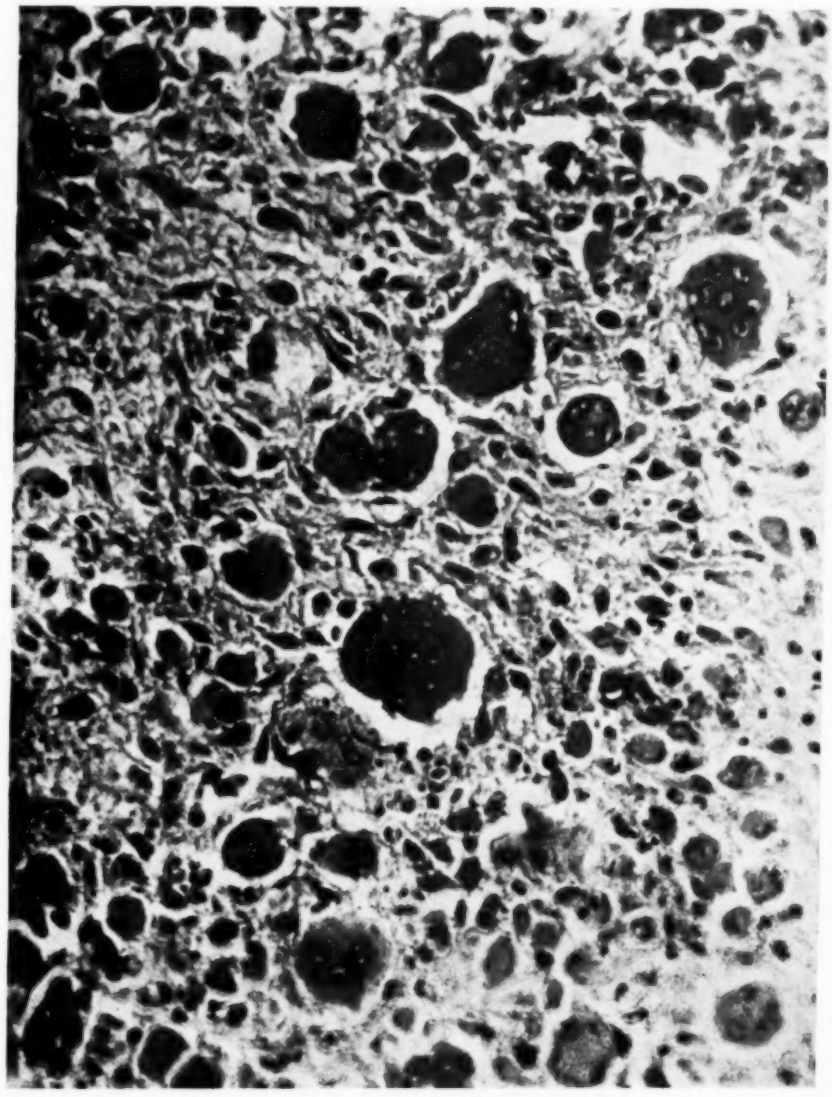

Fig. 15. Group 3. High power section of tumor from chick No. 2, showing characteristic features. Note the large tumor giant cells in loosely woven cellular stroma.

Gross description, chick No. 3. Sections show a very cellular tumor consisting mainly of rounded and polyhedral cells, with prominent highly chromatic nuclei which are eccentrically placed. There is very little intra-cellular stroma. Throughout the sections are seen occasional scattered giant cells of the tumor type. *High power section* (Fig. 2). Bone (tibia) shows considerable thickening and irregular destruction of the cortex. Tumor

mass encircles the whole upper ¾ of the tibial shaft. Tissue appears greyish white, and cuts with considerable resistance.

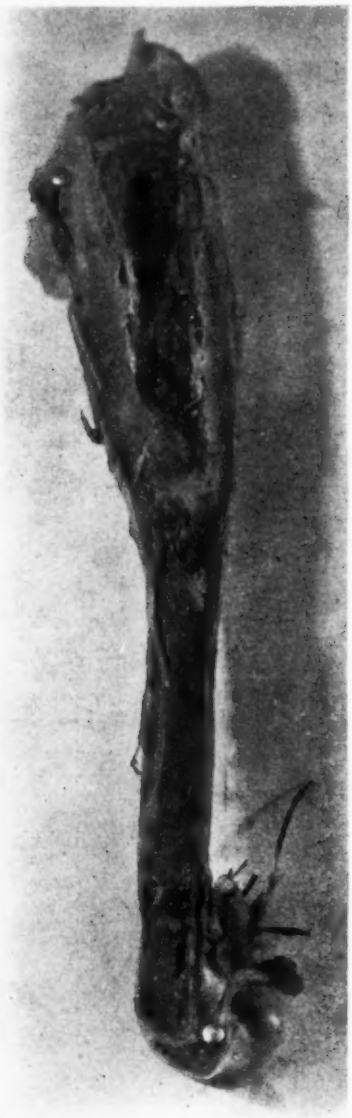

Fig. 16. Group 3. Gross specimen from Chick No. 4, showing bone destruction and soft tissue involvement.

Both lungs showed diffuse nodular metastases. A few whitish nodules seen in the liver, similar histologically to bone picture. Other organs were apparently free from involvement.

Figure 3 is a moderate high power section showing metastases in the lung from chick No. 3. The cells appear to be of the same type as those seen in the original bone lesion.

Figure 4 is the high power section showing the growth in the liver of chick No. 9. Histologically the picture is that of an epithelial growth and differs markedlyf rom that seen in the primary bone lesion. The neoplasmis characterized by masses of cells arranged in broad branching tufts and strands separated by fine connective tissue. The nuclei stained red; the csytoplasm is faintly stained and finely granulated.

Report by Dr. A. P. Stout.[1] Microscopic. "Sections show that the tissue must have undergone considerable autolysis for it stains very poorly and shows on one margin a bit of liver. Adjacent to this is a large tumor mass composed of long tortuous strands of cuboidal cells which seem to lie loosely in spaces in a stroma of loose fibrous tissue. The cells are in an advanced stage of degeneration. They have nuclei which stain bright red. The cytoplasm is granular and vacuolated. With fiber stains it can be demonstrated that there are no fibers between the cells. In the stroma are many mononuclear inflammatory cells with large acidophilic granules in the cytoplasm. The picture is that of a malignant tumor, but it appears much more like a carcinoma than a sarcoma." The diagnosis of carcinoma has been confirmed by Dr. J. E. McWhorter and Dr. F. W. Stewart of the Memorial Hospital.

Figure 5 is a silver stain preparation in chick No. 9, demonstrating the scanty fibrous elements of the tumor seen in Figure 4.

Figure 6 is a high power section from a metastatic carcinoma involving several long bones in the human which shows the similarity of the tumors seen in Figure 4.

Group 2.

In Figure 7 we have the *x*-ray appearance of several tumors produced in group 2. Various types of reaction are noted in the different specimens, some showing expansion and thinning of cortex, others showing

[1] Pathologist to the Presbyterian Hospital, Medical Center, N. Y. C.

both expansion and thickening of the cortex.

Figure 8 is a high power section of the bone tumor from chick No. 4, showing masses of polyhedral or short spindle type of cells with hyperchromatic nuclei in a very loose connective tissue stroma. Throughout the section, numerous blood vessels are seen, many of which appear to be lined by tumor cells. There are a few rather large spaces lined with a thin layer of endothelium and tumor cells. No giant cells are noted in this section. Cells appear to be of the endothelial type.

Figure 9, a medium power section of tumor in bone chick No. 17, shows a compact mass of cells completely replacing the normal medullary tissue and invading and destroying the endosteum. The lacunae in the bone are filled with the tumor cells. There are a few scattered giant cells seen throughout the section. There is very little evidence of new bone formation. Cells appear to be of endothelial type.

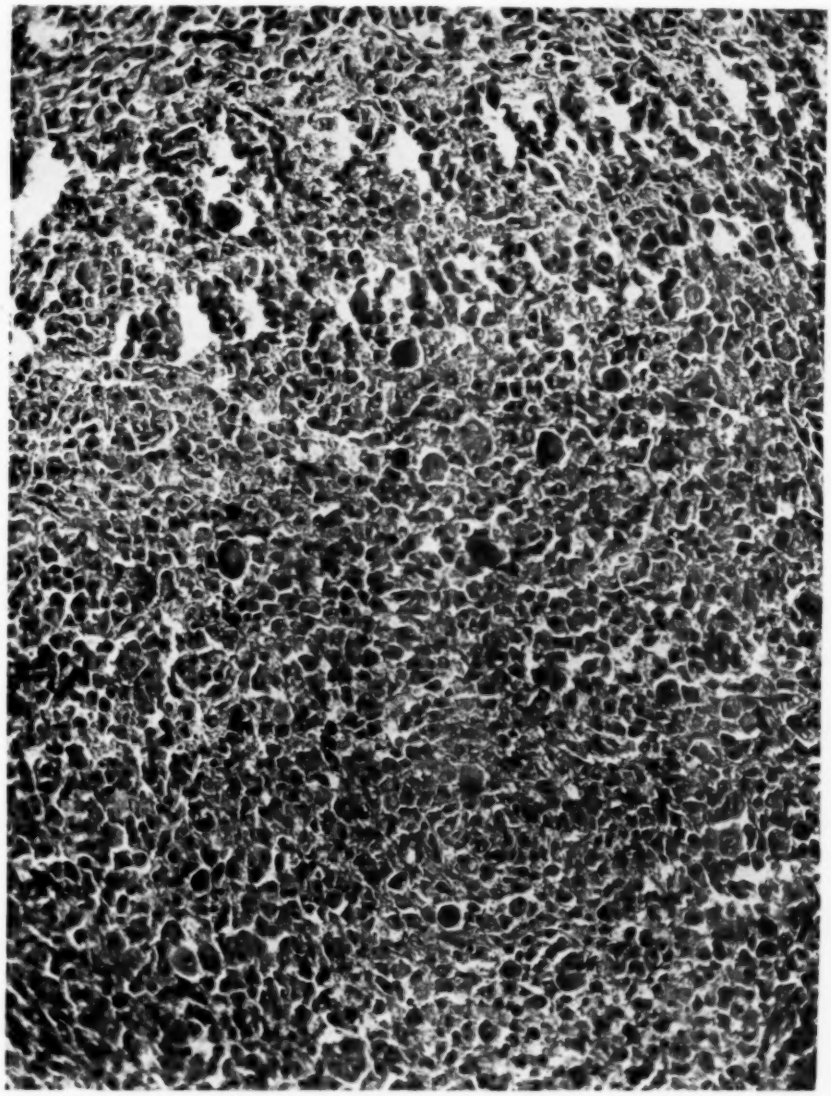

Fig. 17. Group 3. High power section of tumor in chick No. 4, showing closely packed cells of the plasma type. Occasional giant cells are seen.

Figure 10 shows the gross specimens of chicks No. 17, 5, and 1. Note the marked bone destruction in the region of the tumor in No. 17. The tumor was of grayish white

hue firmly attached to and invading the bone, with evidence of cellular growth extending well into the medullary cavity

Fig. 18. Group 3. *x*-ray of tumor in chick No. 3, showing bone destruction, and production in laminated lines closely resembling the Ewing type.

on both sides of the central location. Specimens 5 and 1 show varying degrees of bone involvement, the cortex being almost completely destroyed in No. 1 as shown in the specimen and being replaced by tumor tissue.

Figure 11 is an *x*-ray showing the bone involvement in chick No. 6 in which the upper half of the tibia shows marked new bone and cartilage formation, radiating spicules of bone and varying degrees of destruction throughout. The soft tissue tumor can be well demonstrated when compared with the opposite leg. This appears to be a typical osteogenic sarcoma.

Figure 12 shows a low power section of the tumor shown in Figure 11. The remaining cortex can be seen in the center of the picture with marked proliferation of new bone and tumor tissue radiating at right angels to the shaft.

Chick No. 6 on *gross examination* showed two well-developed bone tumors, one of which developed at the site of inoculation in the upper end of the right tibia, the other arising spontaneously in the tarsal bone of the same side. Grossly, both appeared to be identical in structure and new bone production. There appeared to be considerable cartilage throughout the mass. The lungs showed metastatic nodules ranging in size from 0.75 cm. to fine pin point nodules. Marked emaciation was noted. Nodules in lungs were histologically similar to the bone lesion.

The high power picture (Fig. 13) of a spontaneous tumor arising in a tarsal bone of chick No. 6, shows it to be histologically identical to that seen in the primary tumor arising in the tibia (Fig. 12). Tumor is characterized by marked new bone production with an abundance of spindle cells filling the spaces between the trabeculae. The nuclei of these cells are hyperchromatic and appear to be of the rapidly growing type. New bone is for the most part laid down in disorderly fashion but tends to form in seemingly parallel lines. Picture is histologically comparable to that seen in the human osteogenic type of sarcoma.

Group 3.

Figure 14, *x*-ray of chick No. 2, group 3, shows the bone involvement and the soft tissue tumor anterior to the knee joint arising from inoculation with filtrate from chick No. 6 of group 2 (osteogenic). There is some thinning but very little expansion of the cortex of the bone; a few vacualated or cystic areas can be seen in the upper end

of the tibia. Soft tumor connected with tumor at upper end of the tibia.

Figure 15, a high power section of the elongated and fusiform. A few scattered round cells are seen in some of the sections.

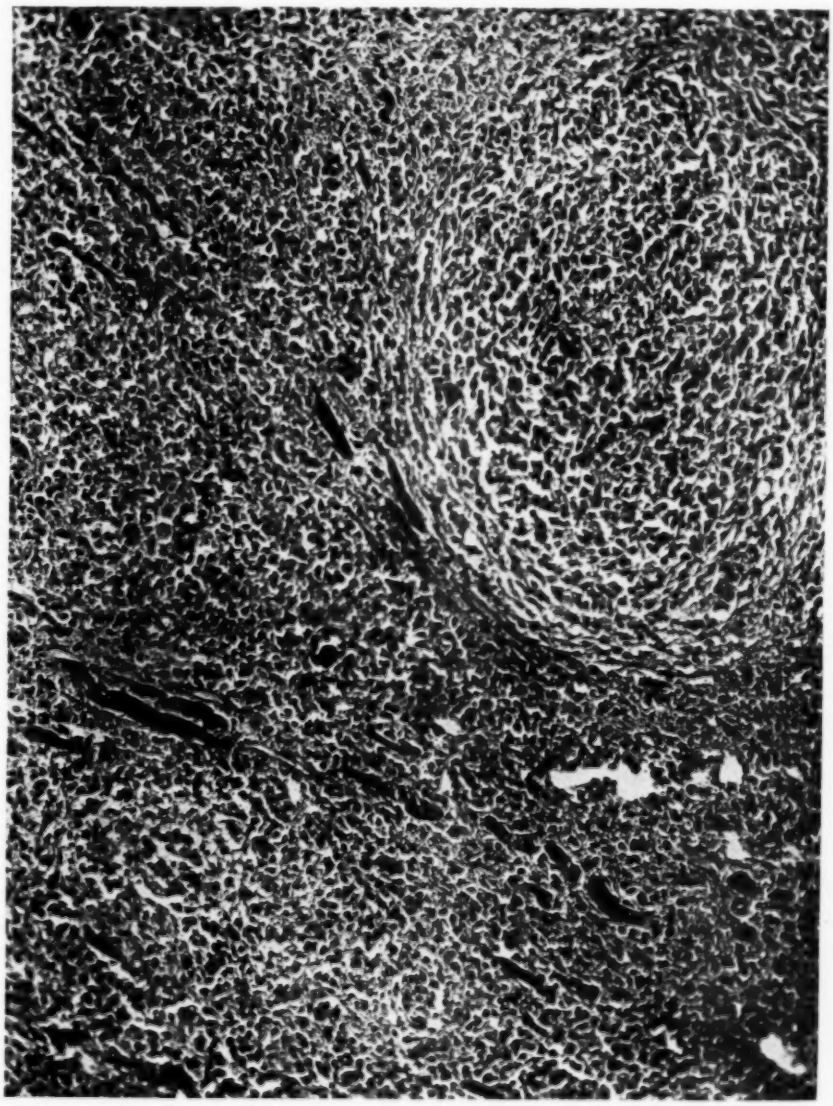

Fig. 19. Group 3. Medium high power section of tumor seen in Figure 18. Note similarity to picture seen in Ewing type of sarcoma. Chick No. 3.

tumor seen in Figure 14, chick No. 2, group 3, shows an exceedingly cellular stroma consisting largely of fine connective tissue fibrils; profusely scattered throughout the latter are many large giant cells, the structure of which rather closely resembles those associated with the giant cell tumor seen in the human. Many of the giant cells show as many as twenty nuclei. These cells are for the most part rounded or oval in shape, although some of them are

Figure 16 shows the gross specimen of chick No. 4, group 3. The great amount of bone destruction can be noted with invasion of the medullary cavity by the tumor cells, which can be seen connected with the extracortical tissue through a break in the shell of bone. No metastatic nodules were noted in this particular case in the liver or lungs. Chick died on the twenty-third day after inoculation with marked wasting of all the skeletal musculature.

Figure 17, a high power section of the tumor in chick No. 4, group 3, shows a very dense cellular matrix of closely packed

Fig. 20. Group 3. Typical breast tumor developed in group 1. Chick No. 3.

rounded or polyhedral cells with eccentric hyperchromatic nuclei and finely granular cytoplasm. Cells appear to be similar to the plasma cell type. There are a few giant cells present which for the most part have two or three nuclei. In some areas the sections show a few embryonal cartilage cells and the endosteum of bone appears to be undergoing destruction and regeneration.

Figure 18 is an *x*-ray picture of chick No. 3, group 3, showing a bone involvement. In the upper third of the tibial shaft is a rather sharply demarkated area of diminished density showing quite distinct striations. The cortex is thin but not markedly expanded and in the lower aspect of the tumor appears to be broken through and connected with the soft extracortical mass. New bone is being laid down throughout the section.

Gross Pathology. Chick No. 3. The bone specimen showed a marked thickening about the upper half of the right tibia. The tumor mass was deeply attached to the bone and nonfluctuant. On section the cortex appeared to be broken in several areas and through these channels the cellular element infiltrated the soft tissues. The bone destruction was more marked than the *x*-ray would suggest. No tumor nodules were seen grossly in the lungs or liver but there was a marked degree of wasting of all the skeletal muscles. Chick died on the twenty-ninth day after inoculation.

Figure 19, a medium high power section of tumor from chick No. 3, group 3, shows a diffusely infiltrating mass of rounded and polyhedral cells having a somewhat mosiac arrangement. These cells are arranged in whirls and circular masses. Some of the masses are arranged around the central blood vessel or sinus. The general appearance of these cells and their arrangement strongly suggests endotheliol origin. In these respects the tumor closely resembles Ewing's sarcoma.

Figure 20, Gross specimen, shows the breast tumor developed in the first group of chicks. The nodules in the liver are rather indistinctly shown in the figure. The bone tumor had been removed for pathological study.

PATHOLOGICAL SUMMARY

Practically all of the chicks in which bone or breast tumors developed showed metastatic nodules in the lungs and liver. The typical lesions have been described in the legends to the illustrations. All of the chicks showed marked wasting of the skeletal musculature. It is interesting that in the Ewing's type, the Giant cell type, and the plasma cell type seen in group 3, the nodules were not noted on necropsy. As has been pointed out, most of the chicks developing tumors died within a period of from fourteen to thirty-three days.

No spontaneous disappearance of either breast or bone tumors was noted. One spontaneous fracture was noted in Chick 4 of group 2 (Fig. 7).

CONCLUSIONS

In summarizing the results of this set of experiments two important facts are presented.

1. The artificial production of malignant tumors derived from filtrates of dried tumor tissue.

2. From the artificially produced tumor tissue filtrates, other malignant tumors have been produced which are dissimilar in respect to morphology, histology and dissemination of metastatic nodules.

3. Culture of dried tissue, and filtrate on usual media showed no growth, but on special media positive cultures were obtained in all tubes with the dried tumor tissue (6), and one showed growth with the filtrate.

The tumors produced have been classified from *x*-ray, gross, histological, and clinical examinations in the following types:

1. Endotheliomas,
2. Endothelial myeloma.
3. Osteogenic sarcoma.
4. Giant cell tumor.
5. Epithelial tumor.

The author wishes to express his appreciation and gratitude to Dr. W. E. Gye who so kindly furnished the original dried tumor tissue used in this work; and to Drs. W. B. Coley, J. E. McWhorter, A. P. Stout, R. W. Lewis and the laboratory technicians for their very kind and helpful assistance in preparing this work for publication.

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COMBINED ROENTGENOLOGIC AND CLINICAL DIFFERENTIAL DIAGNOSIS OF BENIGN & MALIGNANT LESIONS OF THE STOMACH*

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ROCHESTER, MINN.

IN Europe, especially on the Continent, the roentgenologist has never forsaken his status as a clinician, and roentgenologic interpretation is made in the full light of the clinical facts. In America, as a rule, the roentgenologist and clinician conduct their respective examinations independently. Save for clinical data which are obvious, such as the age, sex, and general appearance of the patient, the roentgenologist bases his opinion solely on roentgenologic signs. The clinician likewise endeavors, from the anamnesis and physical signs only, to make at least a provisional diagnosis in order that he may select appropriate laboratory tests and examinations. Later, when he has learned the results of these tests, including the results of roentgenologic examination, he canvasses all the data anew, confers as he deems necessary with others who have participated in the examination, and makes the final diagnosis.

An outstanding advantage of this method is that both roentgenologist and clinician are enabled to conduct their primary investigations without prejudice, and are impelled to derive a maximal amount of information solely from them. This plan has markedly stimulated progress in each line of endeavor, and has aided so substantially in improving diagnosis that it is likely to continue in favor. It provides for correlation of all data in arriving at a final diagnosis, and this paper is directed to the necessity of adequate correlation in order to distinguish between benign and malignant lesions of the stomach.

During recent years the profession has sought, by lectures, publications, and radio broadcasts to impress the public with the necessity of frequent medical examinations in order that carcinoma, wherever situated, may be discovered and extirpated at a time when the chance of cure is not hopeless. To the patients who are beginning to respond to this appeal the physician has imposed on himself an augmented obligation to find existing carcinomas, including those of the stomach, with greater accuracy and at an earlier stage than formerly, and to distinguish them from other lesions with greater precision.

Grossly, carcinoma of the stomach may take the form of frank tumor, infiltrative neoplasm without obvious tumefaction, ulcer without manifest proliferation, or ulcerating tumor in which both ulceration and tumefaction are marked. In advanced cases of all four varieties there are typical instances in which roentgenologic signs are fairly decisive. For example, a medullary carcinoma producing a gross filling defect and a palpable mass, an extensive scirrhous carcinoma narrowing the gastric lumen to an irregular funnel, a huge carcinomatous ulcer with a diameter of 3 or 4 cm., or an ulcerating carcinoma with a deep crater encircled by a prominent ridge, is not likely to be confounded with any of the benign diseases. Likewise, in all four varieties there are many instances in which the anamnesis and the clinical examination are reasonably diagnostic. For example, if a patient is of more than middle age, gives a history of vomiting material which has the appearance of coffee grounds, has lost greatly in weight, is patently anemic and cachectic, and has a palpable mass in the epigastrium, a tentative clinical diagnosis of gastric

* Read before the American Gastro-Enterological Association, Atlantic City, N. J., May 4 and 5, 1931.

carcinoma seldom will be wrong. Yet, no matter how emphatic the clinical or roentgenologic evidence alone may be, the other method of examination cannot safely be omitted, and definitely discordant results from these tests call for further investigation.

Even when gastric lesions are extensive and conspicuous the roentgenologist may err occasionally in distinguishing between carcinoma and a benign neoplasm or syphilitic infiltration, or between a large carcinomatous ulcer and a simple ulcer, notwithstanding the application of differential criteria which are usually trustworthy. Massive soft carcinomas are almost invariably single; they are sessile, and produce deep, irregular marginal defects; peristalsis is absent from the region involved. Benign neoplasms are often multiple, usually predunculated, produce smoothly rounded central defects, and do not interrupt peristalsis. Exceptionally, however, any or all of these marks of distinction fail, and a malignant tumor is adjudged to be benign, or the contrary. Extensive infiltrating scirrhous carcinoma most often causes a funnel-shaped deformity, with an irregular lumen, and the affected gastric wall is palpable. Syphilis tends to convert the affected gastric segment into a narrow tube with a relatively smooth lumen of uniform caliber, and the gastric wall is almost never palpable. Yet there are instances in which scirrhous carcinoma, especially the variety sometimes designated fibromatosis, is mistaken for syphilis, or vice versa. An ulcer with a niche exceeding 3 cm. in diameter, although in all other respects it may have the appearance of a simple ulcer, is likely to be malignant, and the roentgenologist would be remiss if he failed to report this probability but, even though rarely, large ulcers sometimes prove to be benign (Fig. 1). In all such extraordinary cases the clinical history, analysis of gastric content, blood count and Wassermann test have an increased significance and may set the diagnosis right. Conversely, an erroneous primary clinical opinion may be corrected by unequivocal roentgenologic data. It is to be emphasized,

Fig. 1. Large ulcer on lesser curvature which, on the basis of its size, should have been malignant. Clinically the history was indicative of simple ulcer. At operation the ulcer proved to be benign.

however, that errors will persist unless coöperation between roentgenologist and clinician is active, intimate, and thorough.

Far more difficult is the determination whether niche-ulcers, not unduly large, or small prepyloric lesions, are benign or malignant. In both groups, roentgenologic distinction, when feasible at all, requires close observation not only of the slighter morphologic changes, but also of the secondary and functional phenomena. Similarly, the clinician is obliged to take cognizance of lesser subjective and objective manifestations, and to weigh them with scrupulous care. Although neither examiner alone can often make positive decisions, he will at least derive an impression as to the benignancy or malignancy of a lesion, and a summary of the facts derived from all sources may show a definite preponderance of evidence on one or the other side.

On an empiric basis, the roentgenologist can assert rather positively that a perforated ulcer, with an accessory pocket

outside the stomach, is benign, and that an ulcer the crater of which is surrounded by an elevated wall is malignant. He can

Fig. 2. Small, perforated ulcer on lesser curvature accompanied by marked spasm. Roentgenologically, it had all the features of a benign ulcer. Clinically it was suspected to be malignant on account of the short history. At operation the ulcer was found to be malignant.

also be fairly confident that a niche ulcer with a diameter greater than 3 cm. is malignant, but niche ulcers of smaller dimensions bear no patent indications of their nature (Fig. 2) and less obvious signs have to be sought and considered. Among such signs are the following:

Most niche ulcers are benign, and on a statistical basis such an ulcer is presumptively not malignant unless atypical features are present. A sharply conical or irregularly contoured niche is suggestive of malignancy; the niche of a benign ulcer is usually regularly hemispherical. A simple ulcer more often has a dense, clearly depicted niche; a malignant ulcer more often has a faintly shadowed ill defined niche. Ulcers on the posterior wall, well away from the lesser curvature, are more likely to be malignant than those on or near the lesser curvature. Ulcers on the

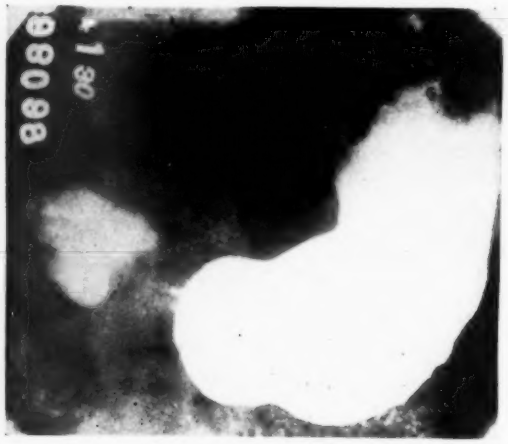

Fig. 3. Concentric prepyloric filling defect and an extensive defect at the cardia. A carcinoma at the cardia and a second carcinoma at the pylorus were discovered at operation. The roentgenologic appearance of the prepyloric lesion is comparable to that shown in Figures 4, 5 and 6.

greater curvature, where they are rare, are almost invariably malignant. Ulcers near the pylorus are more likely to be malignant than those distant from the pylorus. An ulcer with obliteration of the neighboring rugae is probably malignant; an ulcer in the midst of exaggerated and converging rugae is probably benign. Localized gastrospasm is a feature of benign ulcer. An ulcer accompanied by an incisura, antral spasm, a tightly closed pylorus, or spastic retention, is probably benign; a gaping pylorus, or absence of all spastic phenomena, suggests that the ulcer is carcinomatous. Active peristalsis speaks for simple ulcer; faintness or absence of peristalsis speaks for carcinoma. An ulcer on the lesser curvature, in the antral portion of the stomach, accompanied by curling of the curvature and inclination of the bulb toward the median line, is probably not carcinomatous; absence of curling is ground for suspecting that the ulcer is malignant. Sharply localized tenderness over a niche is rather indicative of simple ulcer; a malignant ulcer is seldom tender.

Although small, prepyloric lesions are readily discernible, as a rule they can seldom be identified confidently (Figs. 3, 4, 5, 6). Early scirrhous carcinoma, syphilis, prepyloric ulcer and hypertrophy of the pyloric muscle frequently produce exactly similar deformities. Malignant ulcers and simple ulcers often have no distinguishing marks, and small malignant tumors may assume the guise of those which are benign. Curling up of the antrum, preservation of rugae, active peristalsis, spastic retention and localized tenderness may incline the diagnosis toward simple ulcer. Obliteration of rugae, sluggish peristalsis, a patent pylorus, and absence of tenderness, may suggest that the disease is malignant. But too often the roentgenologist is obliged to content himself with reporting, "lesion at the outlet." In all such cases the clinical factors, combined with the roentgenologic features, may prove helpful.

On the clinical side, contrary to the opinion of certain observers, the majority of benign gastric ulcers present the classical syndrome of ulcer, although not to the same degree and frequency that characterizes duodenal ulcer. About a fourth of all resectable carcinomas, ulcerating and otherwise, temporarily simulate peptic ulcer, especially at the outset, and more than half of all resectable carcinomatous ulcers give rise to the same symptoms, usually over a longer period of time.

Fig. 4. Concentric prepyloric filling defect. A simple ulcer was found at operation. Compare with figures 3, 5 and 6.

Fig. 5. Concentric prepyloric filling defect. On resection the lesion proved microscopically to be syphilitic. See Figures 3, 4 and 6.

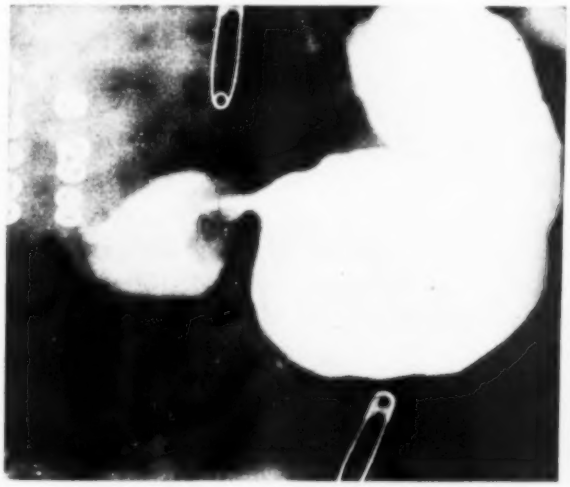

Fig. 6. Concentric prepyloric filling defect, which at operation was found to be due to hypertrophy of the pyloric muscle. Compare with Figures 3, 4 and 5.

Under such circumstances the carcinomatous nature of the lesion, or the transformation of a benign ulcer, may be evidenced symptomatically by one of the

following: (1) disappearance of intermittency of the exacerbation, with substitution of a remittent or continuous clinical course; (2) irregularity, diminution or disappearance of the pain-food-ease sequence; (3) substitution of the usual pain or distress by a dull ache, more or less constant and eventually aggravated rather than eased by alimentation, and (4) loss of appetite and onset of nausea, both of which may ensue, even in the presence of adequate gastric acidity. Objectively, diminution in gastric acidity, disturbance of motor function, onset of anemia in the absence of gross hemorrhage, the appearance, the increase, or the persistence of occult blood in the gastric content and feces during a meat-free regimen are significant. Symptomatic changes are less significant if complications have developed, such as penetration, with involvement of other viscera, extensive perigastric adhesions, and hour-glass deformity. On the other hand, lesions which from a roentgenologic standpoint could be benign may have presented from the onset those symptoms and signs invariably associated with, or characteristic of, frank or even advanced carcinoma.

Although many verified benign gastric ulcers have their onset, at least symptomatically, in the carcinoma age, the combination of advanced age and symptoms of recent appearance should always arouse suspicion of malignancy, even though the lesion may be small. If, also, the anamnesis reveals an irregular or atypical syndrome of ulcer or certain departures from the normal results of analysis of gastric content, or an early tendency to gastric retention or obstruction, the lesion should be regarded as carcinomatous until proved to be otherwise. Judging from our experience, and that of others, the situation of the lesion is of relative significance in differential diagnosis because lesions that are near the pylorus, or on the posterior wall, or near the greater curvature of the stomach, have a greater tendency to be carcinomatous than those on the lesser curvature, or those in the vicinity of the incisura angularis, where most benign ulcers are situated. In the type of lesion under consideration, the general examination is of secondary importance, for only rarely is metastasis recognizable by the examination.

Analysis of gastric content is an indispensable procedure, particularly in debatable cases, and on occasion is the most important link in the diagnostic chain. The usual observations in the frank, advanced, or obstructing form of carcinoma are familiar to all. In our enthusiasm for this procedure as a diagnostic aid, it must be remembered that these familiar data are characteristic chiefly when other diagnostic methods are decisive, or when the condition is obvious. In more than 50 per cent of resectable lesions, and in about 80 per cent of pathologically verified carcinomatous ulcers and small ulcerating carcinomas, free hydrochloric acid is present. In the latter two types, the secretory volume, and the degree of titratable acidity after the alcohol test meal and the stimulus of histamine are usually identical with that of benign ulcer. However, it may be said that hypochlorhydria is the rule, and that the combination of achlorhydria and subacidity is noted in about two-thirds of all cases of carcinoma. The fact that in 60 per cent of resectable lesions, and in 40 per cent of small carcinomatous lesions gastric retention is present is of some significance, especially if this complication develops early in the course of the disease.

With nonobstructing lesions situated on the posterior wall and pars cardiaca, often difficult of visualization by the roentgenoscope, there may be achlorhydria or hypochlorhydria, and blood in the gastric content, and such observation justifies sending the patient back for another roentgenologic examination; the lesion invariably will be visualized after one or more succeeding examinations. Rarely is a gastroscopic examination necessary in these cases. Occasionally carcinomatous

tissue has been recovered from the stomach tube or in the washings. Some of these small lesions, irrespective of their situation, may be accompanied with achlorhydria, blood, lactic acid, or the long bacilli from the outset; thus early differentiation is simple. It should be remembered that in about 5 per cent of all chronic cases of benign ulcer, achlorhydria may be present following a standard test meal and fractional analysis, whereas gastric retention and pyloric obstruction is not uncommon in both benign and malignant lesions, although the incidence is several times greater in the latter.

Constitutional and hereditary factors come in for some consideration, but much remains to be learned in this regard. Carcinoma has a predilection for persons whose constitution may be regarded as normal, or almost normal. Previous good health and digestion are characteristic of the majority of patients with primary gastric carcinoma. If the patient in a given case presents a family history of many carcinomas in several generations, one is inclined to regard the lesion as actually or potentially malignant, and to favor radical methods of treatment.

The results of observation in hospital and adequate medical treatment in difficult cases are often decisive in determining the true nature of the lesion, which is not possible by cursory examination in the consulting room. It may be taken for granted that lesions which undergo complete anatomic restoration and symptomatic recovery, are benign. Failure to achieve this result, however, does not signify that such lesions are carcinomatous, for complications of various kinds, often determinable before or in the course of treatment, may forestall cure in about 40 per cent of cases. In the remainder, the lesion will prove to be malignant. Since it is impossible to distinguish with certainty between the intractable and the malignant lesion, it is essential that surgical interference be undertaken without unnecessary delay.

To summarize, the carcinomatous nature of a small, circumscribed gastric lesion may be evidenced clinically by: change in the character of the clinical course and symptoms, progressive anemia in the absence of gross hemorrhage, loss of weight and strength that is out of proportion to reduction in aliment, a combination of advanced age and recent symptoms, early gastric retention and achlorhydria, or even free acid in the presence of obstructing juxtapyloric lesion, without visible filling defect, blood in the gastric content and persistent achlorhydria, residuum in a fasting stomach in the absence of retention of barium for six hours, occurrence of many instances of carcinoma in several generations, and failure to secure anatomic restoration and symptomatic relief by adequate treatment.

Clinical differentiation of gastric carcinoma from benign gastric tumor is beset with many difficulties for there are many features, differing only in degree, that are common to both lesions. Roentgenoscopic examination as a routine, with a growing familiarity with this type of disease, is largely responsible for the increasing number of individual cases reported from various sources. Clinical features which help in the diagnosis of benign gastric tumors, and which help to distinguish them from malignant gastric tumors are: (1) low incidence, for the ratio of benign to malignant tumors is 1 to 200; therefore, when in doubt, the law of probability would largely favor the diagnosis of carcinoma; (2) absence, or mildness, of dyspeptic symptoms, coupled with good nutritional state and low incidence of obstruction and palpable mass; (3) anemia and gastro-enteric hemorrhage as the outstanding and often the sole symptoms or signs; gross hemorrhage is unusual in gastric carcinoma, especially early in the course of the disease; secondary anemia, rarely a primary form, in the absence of hemorrhage, may be the only feature noted; in fact, anemia is the most common symptom and sign; (4) normal

gastric acidity and secretory volume; this is a common observation, and (5) the age of the patient; several of the largest tumors were in children. Therefore, the benign nature of the tumor may be indicated by these characteristics, usually present in combination, especially when they are combined with the roentgenographic delineation of a lesion exhibiting the signs previously described.

To distinguish gastric syphilis from other gastric lesions, particularly carcinoma, usually requires the closest cooperation between the roentgenologist and internist or syphilologist. The disease is extremely rare, occurring on the average only three times in every 1,000 patients with syphilis in our series, and when gastric syphilis was present, neurosyphilis, carcinoma and duodenal ulcer were more frequently the cause of gastric malfunction than was the specific lesion. The symptom-and-sign syndromes are not infallible, evidenced by the fact that many of the authentic cases were diagnosed roentgenologically as carcinoma. Clinical criteria, exclusive of those based on the effect of antisyphilitic treatment and adequate follow-up observation, also have their shortcomings because of subjective and objective features common to both gastric syphilis and carcinoma, and in lesser degree, to benign ulcer. Moreover, recognition of clinical evidence of syphilis is less significant in the diagnosis of gastric syphilis than is the presence of concomitant data in favor of the other two types of lesion, because the incidence of positive clinical signs of syphilis was almost as high among patients who had syphilis and gastric carcinoma or gastric ulcer as among those with gastric syphilis.

We are here chiefly concerned with the differential diagnosis of syphilitic, benign, and small carcinomatous ulcer, for we are more familiar with the differential aspects of extensive lesions producing filling defects which so closely simulate gastric carcinoma. The small, circumscribed roentgenoscopically visualized lesion, if the patient has syphilis, may be benign, carcinomatous or syphilitic. In our experience it is very uncommon for a circumscribed syphilitic lesion to mimic benign gastric ulcer, symptomatically or objectively. Gastric lesions of a chronic recurring nature, in the presence of the characteristic syndrome of gastroduodenal ulcer, and with adequate acidity, are invariably benign and not etiologically linked with the systemic infection. However, fairly authentic cases of gastric syphilis, with a niche and free hydrochloric acid in the gastric content, have been reported. The small ulcerating carcinoma may give rise to greater difficulty in diagnosis, for in its symptoms, roentgenologic appearance, and nature of the gastric content, it may be indistinguishable from syphilitic ulcer. In such cases, satisfactory differential diagnosis is possible only by abdominal section and histopathologic study of the excised or resected lesion, or by drawing the logical conclusion that the ulcer is actually syphilitic if the defect disappears and symptomatic recovery follows antisyphilitic treatment.

A better understanding as to the frequency with which syphilitic ulcers of the stomach may present themselves with roentgenologic and clinical characteristics indentical with, or approximating, those of benign ulcers and small carcinomatous ulcers, is possible only by regarding every circumscribed gastric lesion of a patient with syphilis as syphilitic in nature until proved otherwise. Judging from our experience, this phenomenon is rare, for in only two cases was it present; in one case it was verified at operation and in the other cure was effected by treatment. On occasion, multiple, contiguous, benign gastric ulcers may produce the same filling defect as carcinoma, and when this occurs in a case in which the patient has syphilis, errors in diagnosis are excusable. Even under such circumstances, the symptoms and chemical changes in the gastric content in cases of benign ulcer usually present themselves, which with satisfac-

tory results obtained from treatment on the basis of a benign ulcer, may deter the circumspect clinician from error.

It is from such roentgenologic and clinical data that distinction between benign and malignant disease often must be made, if it can be made at all. Every case constitutes an individual and novel problem, for the signs and symptoms vary endlessly in their emphasis, in their combinations, and in their weight in particular circumstances. Through the years, efficiency in the diagnosis of carcinoma has increased progressively, but the complexity of interpretation has also increased. Further advances can be made only by discovering new methods of investigation, by more intensive cultivation of those now at hand, or by more thorough correlation of facts at present obtainable. This paper has been devoted to the third alternative. There is no implication that either clinician or roentgenologist should invade the province of the other. On the contrary, we earnestly believe that they should continue to limit themselves to their respective fields and develop them further toward perfection. But it is felt that this separation is sometimes too rigidly practiced, that communication between them is too often restricted to a brief formal report in which neither examiner will venture beyond facts of which he is certain, and that the less definite impressions should not be discarded, but compared and discussed in personal conference. From such conference may come an illuminating reëxamination, a more explicit opinion, or a specific and accurate diagnosis.

DISCUSSION

Dr. M. Feldman (Baltimore): The last cases Drs. Eusterman and Kirklin showed are those that are well advanced. The differential diagnosis between ulcer and cancer becomes increasingly more difficult in the early stages. This is true both from a clinical as well as a roentgenological standpoint. Roentgenologically we depend principally upon the presence of a filling defect in the diagnosis. The filling defect is usually characteristic and presents itself in the forms Dr. Kirklin showed; one as a projective type and the other as an invading type defect. There is, however, a certain percentage of cases which do not reveal the usual pathognomonic filling defect and in order to make a diagnosis one must rely on the secondary signs, especially in the early cases. By grouping these signs with the clinical picture and other laboratory tests an early diagnosis is possible in many instances.

I would like to emphasize the importance of repeated *x*-ray examinations as especially necessary in the study of gastric lesions.

Dr. Sara M. Jordan (Boston): It seems to me that this paper is very important as showing the necessity for cooperation between the roentgenologist and the clinician; not only, however, to make the diagnosis when the patient first comes in, but also to follow the patient along during the necessary medical management in borderline cases. We have found that a great many cases fall in the group which are borderline, neither out-and-out carcinoma nor out-and-out ulcer. If we put them in the hospital and put them on a definite regime of medical management for a period of time, usually not more than two weeks (rarely two weeks; it is usually about a week or ten days) we find that three things must occur if we are to assume that these patients have benign ulcer.

First, that the lesion must disappear by *x*-ray. There must be no evidence of a deformity.

Second, that occult blood must disappear from the stools.

And third, that the patient must be completely relieved of symptoms.

I said that it was necessary to prove that the patient had a benign ulcer. I should add that some of the benign ulcers heal to the point where the radiological defect is just a dimple. But that dimple remains there and these cases later turn out to be benign but recurrent ulcers. In those cases we also advise surgery because we do not like the patient to go out with an ulcer defect which we think indicates a future recurrence of trouble.

Regarding the size of the lesion, I was very much intimidated several years ago by two very large lesions on the lesser curvature side of the stomach which because of their size seemed to me suspicious of malignancy. But these lesions disappeared completely and the patients are well today after several

years. So we feel the size of the lesion is not one of the criteria to which we must pay attention.

Regarding prepyloric deformity, that has given us a good deal of difficulty because it may be due to either spasm or ulcer or carcinoma or carcinomatous ulcer, and it is in some of the cases with spasm that we have had considerable question. Patients have been sent to us from roentgenologists with a diagnosis of carcinoma at the pylorus and after a week of treatment that carcinoma has proved to be nothing, the stomach then being entirely normal and the original deformity having been due to spasm.

Dr. W. L. Palmer (Chicago): I should like to emphasize the fact that *x*-ray is, after all, merely an adjunct of medicine, one of the diagnostic methods at our disposal. Before making the final diagnosis, the internist should have at hand not only the report of the *x*-ray findings, but also the films, and, more important still, the privilege of fluoroscoping the patient himself. The diagnosis should be based upon all of the evidence available, clinical, laboratory and roentgenologic.

As far as *x*-ray findings are concerned, I think we should insist upon direct signs of carcinoma, the direct signs of ulcer. It seems to me the findings the second speaker mentioned, the secondary findings of carcinoma, are really direct findings of carcinoma: the rigidity or fixed condition of the lesser curvature.

I would like to ask two questions. One, of Dr. Kirklin, whether he is sure belladonna will relax gastric spasm. And the other one of Dr. Eustermann: how accurately is it possible for the internist with closest cooperation of the roentgenologist to differentiate between benign and malignant gastric lesions?

Dr. H. L. Bockus (Philadelphia): There is one thing I should like to mention and that is the necessity for keeping the pyloric ulcer segregated from the other types of stomach ulcer. I have had 3 cases which have recently been reported with a sizeable gastric ulcer above the incisure on the lesser curvature associated with marked six-hour gastric retention. In the older textbooks on roentgenology six-hour retention was mentioned as a frequent finding in gastric ulcer without attempting to differentiate between corporic ulcer and ulcer near the pylorus. These 3 cases which have been reported had a carcinoma at the pylorus accounting for the retention and a gastric ulcer in the body of the stomach. And the thing which led us particularly to suspect the possibility of another lesion accounting for the retention was the fact that the retention did not subside after medical treatment. We have had a number of cases of gastric ulcer of the body of the stomach with gastric retention in which a second lesion was found at the pylorus which proved to be a duodenal ulcer. It is of interest to note that in two of these cases with malignancy at the pylorus the gastric acidity was either normal or hypernormal.

Dr. B. R. Kirklin (closing): Cases similar to those discussed by Doctor Feldman emphasize a point which I think is extremely important; namely, that it is essential to examine these stomachs with a small amount of barium and with careful manipulation, to approximate the gastric walls during roentgenoscopy.

Doctor Cole mentioned the importance of serial examination, and I heartily agree with him. I am sure Doctor Eusterman feels that if these patients are studied after treatment, and the niche disappears, malignancy can be ruled out definitely.

I think it is only by independent examination by the roentgenologist and by the clinician, especially by the roentgenologist, that we in America have been able to attain such accuracy in the diagnosis of gastric lesions. At the clinic the roentgenologist knows nothing of the clinical story of the patient. We do not want to know the results of the clinical examination until our examination has been completed. Then we want to know all we can find out about them, and to correlate the facts with our roentgenologic data. A member of the roentgenologic staff is present at the operation to see what is found. It was Carman who started this procedure at the clinic, and it was only by careful correlation of all the data that we have been able to attain whatever accuracy we enjoy.

As to the efficacy of belladonna in combating spasm, I feel that reëxamination may have more influence than the drug. Often, at the first examination, the patient is frightened by his somber surroundings and the garb of the attendants, and makes all his muscles tense. At the second examination he is more familiar with the environment, is less appre-

hensive, and relaxes more readily. Possibly this plays a larger part than belladonna.

Dr. George B. Eusterman (closing): I think it is a little unfair for the roentgenologist to expect too much of a clinician, especially in those cases seen only in routine consulting-room practice. Of course, it is a good idea for the clinician, if he wishes to improve his diagnostic acumen, to render a tentative opinion after the history has been taken and examination made before the laboratory reports are in. We all realize the difficulty in differentiating between gastric and duodenal ulcers clinically. This can only be done successfully in a small group of cases. The roentgenologist, if he visualizes a lesion, can do it, and so can the surgeon at the operating table, but it is too much to expect of a clinician. He may diagnose ulcer with conviction, but to locate it is another matter. It is not difficult to diagnose the ordinary form of gastric carcinoma in most instances, when one considers the fact that half of these are inoperable at the time we see them. The clinician may also have evidence that the condition is inoperable although it may appear operable to the roentgenologist.

Regarding the question raised by Doctor Palmer, if I understood him rightly, I think that in some cases we can absolutely say that a lesion of the pylorus is malignant, especially in association with achlorhydria and retention. These differential features are brought out in the paper. It must be remembered that in about 5 per cent of all benign gastric ulcers, usually those of the corpus, a relative achlorhydria may be present and the lesion still be benign. In the absence of surgical exploration and microscopic diagnosis one can only determine the nature of the gastric lesion by the way it behaves under adequate treatment over an adequate period of time, yet Jordan has shown that a considerable percentage of gastric lesions may not fulfill all the requirements of benignancy as the result of treatment and still be benign when removed and examined microscopically.

FACTORS INFLUENCING PROGNOSIS IN THE MEDICAL TREATMENT OF DUODENAL ULCER*

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ALTHOUGH statistics on the results of treatment of duodenal ulcer are difficult to compile and more difficult to interpret, it has been our experience that of all cases treated medically nearly one half, or 46 per cent, may be expected to have one or more recurrences within five years.

Table 1 indicates that the incidence of recurrences is 9 per cent at the end of the first year and that this incidence increases year by year until at the end of five years only 54 per cent of the patient have had an uninterrupted remission since they were treated.

TABLE 1

CLINICAL RESULTS IN 392 CASES OF DUODENAL ULCER TREATED MEDICALLY

Duration of Follow Up	One Year	Two Years	Three Years	Four Years	Five Years
Successful cases	355 (91%)	211 (81%)	121 (70%)	51 (61%)	20 (54%)
Unsuccessful cases	37 (9%)	49 (19%)	51 (30%)	33 (39%)	17 (46%)
Totals	392	260	172	84	37

The lack of any generally accepted standard for what is to be considered a recurrence is one of the difficulties in comparing ulcer statistics and this seemingly high incidence of recurrences in our series is due to the fact that we have classified as cases unsuccessfully controlled all patients with digestive symptoms, apparently due to ulcer which are relatively persistent and severe enough to interfere to any extent with the patient's activity. Many of this group reported themselves as well later. Of course, all frank recurrences of pain, hemorrhage, obstruction and perforations are classified as recurrences. Since the cases recorded as successful are definitely known to have had a remission extending over the number of years indicated, we believe that if there is any error in our figures it is towards making the percentage of recurrences too high rather than too low.

Our method of management in all cases reported here has consisted of neutralization methods (Sippy) with the patients in bed in the hospital for about three weeks. During the hospital treatment the patients are observed carefully and a search made for foci of infection and for other pathological conditions in the abdomen. During part of the following year alternating cream feedings and alkaline powders are given at frequent intervals during the day. The patients are instructed to abstain from tobacco and alcohol and to avoid unusual physical and nervous strain.

Since it is highly desirable to choose a fitting type of treatment for each patient individually, particularly to decide whether medical or surgical treatment is indicated, we have endeavored to determine the factors in the history, physical findings and laboratory data that make it probable that the patient will or will not have a recurrence within five years if he undergoes medical treatment.

* From the Department of Gastro-Enterology, Lahey Clinic. Read before the American Gastro-Enterological Association, Atlantic City, N. J., May 4 and 5, 1931.

With this purpose in mind we have collected 60 cases of duodenal ulcer which have undergone medical treatment in the Lahey Clinic with unsatisfactory results. For the purpose of evaluating certain prognostic points we have subjected the case records of this series to a special analysis and compared them with a series of 60 unselected successfully relieved cases. After the 60 medical failures had been collected it was found that 13 had either deliberately or carelessly failed to follow anything like a satisfactory regime, so that in justice to our statistics we have omitted these from our calculations. (Table II.) The mortality in this series of cases, treated medically, was 0.8 per cent.

TABLE II

CASES OF DUODENAL ULCER SUBJECTED TO COMPARATIVE STUDY

Successful cases	60
Cases unsuccessful	60
(treatment not followed in 13)	
Because of pain	34
Because of hemorrhage	13

Gross hemorrhage into the gastro-intestinal tract is frequently the chief manifestation of failure in treatment. Certain patients appear to be subject to recurrent hemorrhages without any other symptoms. The clinical aspects of the cases with either mild or no other symptoms except hemorrhages are so different from the type of failure with pain, obstruction, or vomiting, that for the purpose of more careful analysis they have been analyzed separately. Of the 47 medical failures in the series, 13 fall into the classification of failure due to painless hemorrhage. Throughout our comparison of certain clinical and laboratory features we have recorded separately the three following groups: successful cases, cases unsuccessful because of recurrence of pain and cases unsuccessful because of hemorrhage without significant pain or distress.

A history of hematemesis or of the passage of tarry stools was obtained in 15 per cent of our successful cases and in 55 per cent of the unsuccessful cases (Table III). In the cases which failed because of recurrent pain, 26 per cent gave a history of hemorrhage, while among those which failed because of hemorrhage 77 per cent had a history of hemorrhage before coming to us. A history of two or more previous hemorrhages was obtained as follows: in successful cases, 1.6 per cent; in cases unsuccessful because of pain, 2.9 per cent; and in cases unsuccessful because of hemorrhage, 46 per cent. In 386 cases of duodenal ulcer, a history of gross hemorrhage was given in 19.4 per cent, including 4.4 per cent who had had two or more hemorrhages. The relatively much higher incidence of hemorrhage, particularly repeated hemorrhages in cases which eventually prove to be unsuccessful, indicates that this point is of considerable prognostic value in estimating the probability of success or failure of medical treatment. The importance of two or more hemorrhages is strikingly brought out when the follow-up reports of cases with this history are compared with the results of cases without such a history. This table shows that in 386 cases of duodenal ulcer, there were 58 cases which gave a history of one hemorrhage. Of these, 16 or 27 per cent experienced a relapse within three

TABLE III

THE INFLUENCE OF A HISTORY OF GROSS HEMORRHAGE ON END RESULTS

	One Hemorrhage	Two or More Hemorrhages
60 successful cases	13.4%	1.6%
47 cases unsuccessful	40.4%	14.9%
Because of pain (34)	23.1%	2.9%
Because of hemorrhage (13)	31.0%	46.0%
386 cases of duodenal ulcer	15.0%	4.4%

	No Hemorrhage	One Hemorrhage	Two or More Hemorrhages
Series of 386 cases followed one to five yrs.	311	58	17
Successful	266 (83%)	42 (73%)	3 (18%)
Unsuccessful	45 (17%)	16 (27%)	14 (82%)

years with a recurrent hemorrhage the cause of failure in 9 cases. Of 17 cases which had had more than one hemorrhage before treatment, fourteen or 82 per cent had a recurrence of symptoms which in 12 of the 14 consisted of hemorrhage.

The symptom of vomiting was recorded as present only when it was an outstanding feature usually associated with gastric retention (Table IV). The fact that vomiting and six-hour retention of barium occur over three times as frequently in unsuccessful as in successful cases, shows that they are indications of the severity of the ulcer.

TABLE IV

VOMITING AND SIX HOUR GASTRIC RESIDUE

	Vomiting	6 Hour Gastric Residue
60 successful cases	15%	10%
47 cases unsuccessful	36%	30%
Because of pain (34)	50%	41%
Because of hemorrhage (13)	0%	0%

There is apparently no striking difference in the severity of the pain or its radiation in the successful cases and in those which had a recurrence of pain after treatment (Table V). Night pain and distress, however, are almost twice as common in the unsuccessful group. Pain in the hemorrhage cases is noticeably mild or absent.

TABLE V

PAIN

	None	Mild	Moderate	Severe	Very Severe
60 successful cases	0%	60%	32%	6%	2%
47 cases unsuccessful	4%	49%	34%	11%	2%
Because of pain (34)	0%	38%	44%	14%	3%
Because of hemorrhage (13)	15%	77%	8%	0%	0%

Radiation to Back And Chest

Recorded in	
54 successful cases	37%
45 cases unsuccessful	20%
Because of pain (32)	25%
Because of hemorrhage (13)	8%

Night Pain

Recorded in	
52 successful cases	36%
41 cases unsuccessful	49%
Because of pain (28)	61%
Because of hemorrhage (13)	22%

At the first physical examination there were few physical findings which proved to be of prognostic importance (Table VI).

TABLE VI

PHYSICAL EXAMINATION

EPIGASTRIC TENDERNESS

Recorded in	
49 successful cases	22%
41 cases unsuccessful	34%
Because of pain (28)	50%
Because of hemorrhage (13)	0%

However, epigastric tenderness was twice as common in the cases which later had a recurrence of pain, as in the successful cases.

The gastric acidity was determined by the titration of the free and total acidity in the gastric contents obtained forty-five minutes after the ingestion of an Ewald test meal (Table VII). The results of the first examination show that the finding of a high, normal, or a low gastric acidity is of little prognostic importance because they occurred in both groups in about the same proportion of cases. In most of the cases the test was repeated every few months during the two years after the treatment was started (Table VIII). It was found that in 56 per cent of the successful and in 77 per cent of the unsuccessful cases the acid secretion after a test meal remains the same as it was before treatment. In about 8 per cent of both groups there is even a tendency to an increase in acid secretion. However, in 36 per cent of the successful cases there was a definite tendency towards a decrease in acid secretion as compared to 15 per cent of the

TABLE VII

GASTRIC ACIDITY

	Free HCl of 60 or over	Free HCl between 40 and 60	Free HCl under 40
60 successful cases	40%	29%	31%
47 cases unsuccessful	36%	49%	15%
Because of pain (34)	41%	41%	18%
Because of hemorrhage (13)	23%	69%	8%

unsuccessful cases showing this tendency before there was a recurrence.

The resistance to neutralization of the gastric contents with alkali therapy was determined by titrating the unneutralized acid one-half hour after the last powder was given at nine P.M. The results showed that complete neutralization was not obtained and apparently was unnecessary in one-third of the successful cases. Although the unsuccessful group which later had a recurrence of pain showed a much higher percentage, or 61 per cent, of cases with resistance to neutralization, the feature is not sufficiently characteristic to make it important in the prognosis of an individual case.

Table IX

NEUTRALIZATION

	Satisfactory Night Neutralization	Unsatisfactory Night Neutralization
Recorded in		
58 successful cases	66%	34%
42 cases unsuccessful	48%	52%
Because of pain (31)	39%	61%
Because of hemorrhage (11)	73%	27%

The roentgen-ray examination of the duodenum was done by a combination of the fluoroscopic and film methods (Table x). The activity of the stomach was noted and the deformity of the duodenal cap was classified as slight, moderate, marked and "no filling." The comparative results showed that although hyperperistalsis and the degree of deformity of the duodenal cap are indications of the severity of the ulcer, they are of little value in estimating the success of treatment.

Table VIII

EFFECT OF TREATMENT ON THE HCL RESPONSE TO A TEST MEAL

	Persistently High HCl (Over 50)	Persistently Normal HCl (30–50)	Persistently Low HCl (Under 30)	Decreasing HCl (High to Normal)	Increasing HCl (Normal to High)
59 successful cases	24%	30%	2%	36%	8%
39 cases unsuccessful	38%	36%	3%	15%	7%
Because of pain (27)	41%	37%	0%	15%	7%
Because of hemorrhage (12)	33%	33%	8%	17%	8%

The effect of treatment upon the *x*-ray appearance of the duodenal cap, however, is strikingly shown by the subsequent *x*-ray examinations during the two years following the hospital treatment (Table xi). We believe that the disappearance of the duodenal deformity in 70 per cent of the successful cases combined with an improvement of the duodenal outline in 20 per cent more, leaving only 10 per cent unchanged, is of particular significance when compared with 51 per cent with no improvement in the *x*-ray defect among those who later had a recurrence of pain. The fact that the duodenal defect disappeared in some of the cases which later had a recurrence of symptoms shows that the defect was chiefly spasm which was relieved for a while by treatment although

Table X

HYPERPERISTALSIS AND DEFORMITY OF THE DUODENAL BULB

	Hyperperistalsis	Degree of Deformity of Cap			
		Slight	Moderate	Marked	No Filling
60 successful cases	43%	17%	67%	15%	2%
47 cases unsuccessful	60%	21%	55%	19%	4%
Because of pain (34)	71%	12%	59%	23%	6%
Because of hemorrhage (13)	31%	46%	46%	8%	0%

the underlying disease was still unrelieved. On the other hand, the 10 per cent of successful cases showing no change in the outline of the cap as a result of treatment suggests that in some cases the duodenal defect is, in part at least, due to permanent cicatricial contractions. These results indicate that the repeated *x*-ray examination is the most useful and reliable single objective check on the progress of treatment.

Table XI

RADIOLOGIC CHANGES AFTER TREATMENT

	Improvement	Disappearance	No Change
60 successful cases	20%	70%	10%
43 cases unsuccessful	42%	16%	42%
Because of pain (31)	39%	10%	51%
Because of hemorrhage (12)	50%	25%	25%

We found that although gastric retention is four times as common in the unsuccessful cases, its presence does not preclude satisfactory recovery under medical management (Table XII). Even in some of the cases which still had retention at the end of the hospital treatment, the condition improved and the stomach was found to empty in normal time in subsequent examinations. However, persistent retention was three times more frequent in the cases which later had a recurrence of pain.

Table XII

BARIUM RETENTION

	Six Hour Residue	Relieved in Hospital	Not Relieved in Hospital
60 successful cases	10%	5%	5%
47 cases unsuccessful	32%	17%	15%
Because of pain (34)	41%	26%	15%
Because of hemorrhage (13)	8%	8%	0%

Occult blood in the stools was a finding which proved to have some importance in the prognosis of ulcer cases (Table XIII). Slow bleeding into the duodenum is apparently an indication of a severe lesion, particularly if there is a tendency to persist during rest in bed on a neutralizing treatment. There were over four times as many unsuccessful cases with occult blood as successful cases showing this test.

Table XIII

OCCULT BLOOD IN STOOLS

	Occult Blood Present on Admission	Persistence for One Week or More on Treatment
59 successful cases	12%	8%
46 cases unsuccessful	52%	28%
Because of pain (33)	52%	30%
Because of hemorrhage (13)	54%	23%

Alkalosis is a subject of considerable interest since patients are not infrequently encountered who cannot tolerate alkali in the dosage employed in the neutralization form of treatment. (Table XIV.) Thirty per cent is the strikingly high incidence of mild or severe alkalosis shown by these unsuccessful cases as compared with 3 per cent in the successful group and 6 per cent in a large group of ulcer cases treated with alkalies. This confirms the observation that frequently medical failure is caused by the inability of the patient to tolerate sufficient alkali to control his symptoms. We have noted alkalosis rather frequently in a transient form characterized by the onset of the usual symptoms which disappear when alkalies are withdrawn and do not reappear when the powders are resumed in exactly the same dosage. In the second type, which we have designated as mild, the symptoms reappear if the powders are resumed in the regular doses, but the patients are able to tolerate alkalies in somewhat reduced amounts which are frequently found on further observation to be sufficient to control the symptoms. In the severe form no appreciable amount of alkali can be given without the induction of severe symptoms accompanied by nitrogen retention and other marked changes in the blood chemistry. The relatively much higher incidence of alkalosis in the unsuccessful cases indicates that intolerance to alkalies is an unfavorable prognostic sign for the success of medical treatment for ulcer. Of 23 patients who showed definite intolerance to alkalies

and who have been followed for at least a year, 70 per cent had recurrences. (Table XV.)

The prognostic significance of hypertension appears to be related to the intolerance to alkalies because over half of the cases

TABLE XIV
ALKALOSIS

	No Alkalosis	Transient Alkalosis	Mild Alkalosis	Severe Alkalosis
60 successful cases	58	0	2 (3%)	0
47 cases unsuccessful	31	2 (4%)	8 (17%)	6 (13%)
Because of pain (34)	21	2 (6%)	5 (15%)	6 (18%)
Because of hemorrhage (13)	10	0	3 (23%)	0
577 cases of duodenal ulcer	529	12 (2%)	20 (3%)	16 (3%)

Although the causative factors and the mechanism by which they produce alkalosis are still largely undetermined, there are

TABLE XV
EFFECT OF ALKALOSIS AND OF HYPERTENSION ON CLINICAL END RESULTS

23 Cases Showing Mild or Severe Alkalosis (followed for one year or longer)	
Successful	7 (30%)
Unsuccessful	16 (70%)
46 Cases with Hypertension (followed for one year or longer)	
Successful	29 (63%)
Unsuccessful	17 (37%)

distinct clinical associations between this condition and hypertension, arteriosclerosis and chronic vascular nephritis (Table XVI). In a large group of duodenal

TABLE XVI
HYPERTENSION

	Hypertension	Normal Blood Pressure
59 successful cases	5 (9%)	54
43 cases unsuccessful	14 (33%)	29
Because of pain (31)	10 (33%)	21
Because of hemorrhage (12)	4 (33%)	8
572 cases of duodenal ulcer	75 (13%)	497

ulcer patients we found hypertension in 13 per cent, the criteria of hypertension being a systolic pressure of over 150 or a diastolic pressure of over 90. In the group of successful cases studied, the incidence of hypertension was smaller or only 9 per cent, while the unsuccessful cases showed a much higher percentage or 33 per cent.

with either severe or mild alkalosis had elevated blood pressures. (Table XVII.) The relationship between kidney function and intolerance to alkalies is brought out by the fact that out of 36 cases of alkalosis, 9 had elevated non-protein nitrogens in the blood, 5 had other evidences of renal impairment, such as diminished phthalein

TABLE XVII
HYPERTENSION IN 44 CASES WITH ALKALOSIS AND IN 528 CASES WITHOUT ALKALOSIS

	Hypertension	Normal Blood Pressure
Severe alkalosis (14)	8 (57%)	6
Mild alkalosis (18)	14 (78%)	4
Transient alkalosis (12)	4 (33%)	8
No alkalosis (528)	49 (9%)	479

output and fixation of specific gravity, 5 had obstructive urinary tract disorders, such as unilateral hydronephrosis in 3, and bladder neck obstruction in 2. (Table XVIII.)

CONCLUSIONS

In conclusion, therefore, we have found that nearly one-half of all cases of duodenal ulcer treated medically have one or more recurrences within a period of five years after treatment.

About one-fifth of the recurrences can be ascribed to carelessness on the part of the patient.

A little over one-fourth of the remaining recurrences are characterized by gross

hemorrhage which is not associated with pain or other important symptoms.

Among the clinical features which are manifest in the examination and treatment of cases of duodenal ulcer, there are some with important prognostic significance, others with suggestive but inconclusive prognostic value and others which give no aid whatever in estimating the probability of success or failure of medical treatment. (Table XIX.)

Table XVIII

RENAL FUNCTION IN CASES WITH ALKALOSIS

	Nitrogen Retention	Impaired Renal Function	Obstructive Surgical Lesions	Normal Renal Function
Severe alkalosis (16)	6	3	2	5
Milk alkalosis (20)	3	2	3	12
Total	9	5	5	17

Table XIX

SUMMARY

Features with Important Prognostic Significance	Features with Suggestive Prognostic Significance	Features with Little or No Prognostic Significance
1. History of one or more gross hemorrhages.	1. Persistent six hour retention of barium.	1. Age.
2 Intolerance to alkali therapy.	2. Failure of duodenal outline to improve after treatment.	2. Sex.
	3. History of one gross hemorrhage.	3. Age at onset of symptoms.
	4. Resistance to neutralization.	4. Duration of disease.
	5. Persistent occult blood in stools.	5. Severity of pain.
	6. Hypertention	6. Degree of deformity of the duodenal cap.
	7. Epigastric tenderness.	7. Degree of hyperacidity.

The two most important features which are outstanding enough to be useful in planning treatment for the individual case are, first, the history of two or more gross hemorrhages, and second, the demonstration of a marked intolerance to alkali therapy.

Among the features which are characteristically more common in cases who are ultimate failures on medial treatment but are not sufficiently outstanding to make them conclusive indication for or against medical management are: failure of the duodenal cap to show improvement in outline after treatment, the six-hour retention of barium in the stomach particularly if still present at the end of three weeks' hospital treatment, a history of one gross hemorrhage, a marked resistance to neutralization of the gastric contents with alkali therapy, occult blood in the stools particularly if there is a tendency to persist on treatment, and the physical findings of hypertension and epigastric tenderness.

The features which have little or no prognostic value are: age, sex, age at the onset of symptoms, duration of the disease, severity of pain, degree of deformity of the duodenal cap at the first examination if there is no six-hour residue and the degree of hyperacidity after an Ewald meal.

Improvement in the *x*-ray appearance of the duodenal cap was found to be the most reliable single objective test as a guide to medical management.

Alkalosis was found to be associated in a large proportion of cases with hypertension, other evidences of chronic vascular nephritis and with obstructive surgical lesions in the urinary tract.

DISCUSSION

Dr. Julius Friedenwald (Baltimore): In considering the plan of treatment to be instituted in ulcer, the greatest difficulty arises as to the etiology of this affection, which is still obscure. We cannot be content with viewing the disease simply as a local manifestation limited to the stomach or duodenum alone, inasmuch as some systemic disturbance may be largely accountable for the chronicity of the local condition. In a series of 200 of our ulcer cases the following causative factors were noted:

	Per Cent
Infections	42
Disturbances of nervous system	14
Disturbances of endocrine system	4
Hyperchlorhydria	8.5
Trauma	2
Anemia	14
Arteriosclerosis	13
Syphilis	2.5

The etiology of ulcer is therefore extremely complex and it is evident that there may be many causes contributing singly or in combination entering into the production of this affection. In order therefore to secure the best results not only from medical but surgical treatment as well, it is important to determine if possible the presence of all causative factors. It is only in this way that a complete eradication of the disease and a permanent cure can be expected.

In considering the plan of treatment to be instituted in peptic ulcer, one must bear in mind the three clinical types of this disease with which we are confronted, which Crohn has more recently emphasized in his book: the acute form, the recurrent and the chronic continuous type. In the acute type we are usually dealing with younger individuals (rarely beyond forty years) and while the symptoms may be most profound such as hemorrhage, these ulcers show a marked tendency to heal and are usually well controlled by medical treatment. The recurrent ulcers in which there are periods of remission also present periods of healing, even though these be incomplete and scar formation is not perfect. With thorough medical treatment, however, cicatrization may be brought about and permanent healing secured. When this does not occur, chronic ulcers develop, which follow a continuous course without remission and rarely present any marked evidence of healing. In this type, the symptoms are usually progressive and may simulate carcinoma. The pathological process is usually that of a large callous ulcer. Such ulcers may require surgical interference in order to obtain permanent cure.

While the indications for medical or surgical treatment, therefore, are quite definite in some instances, there are many cases occupying the borderline, in which the correct procedure to be followed may remain uncertain. It is often surprising how a very large proportion of cases of duodenal ulcer yield completely to rigid medical treatment and on this account the patient should always be given, when possible, the benefit of such a cure, especially as there is but slight possibility of malignant transition in duodenal ulcer. There is even a definite though small group of cases in which pyloric stenosis occurs as a result of the cicatrization from ulceration in which the symptoms of retention may disappear and in which the motor function of the stomach may be restored to normal or nearly normal by means of medical treatment alone.

I am equally confident that most gastric ulcers will also heal under medical treatment and inasmuch as the incidence of the transition into malignancy of this affection is but slight (not over 6 to 8 per cent), medical treatment should be undertaken except in the obviously suspicious or doubtful cases.

I am also in thorough accord with Dr. Jordan, not to consider surgery indicated as long as the gastric defect continues to diminish in size and gradually disappears and occult blood remains absent from the stools while the patient is under treatment. If this does not occur, operation is indicated.

Finally, I still remain an ardent advocate of at least three to four weeks of hospital bed rest when treatment is first instituted. This not only assures at least a good beginning in the process of healing, when this is at all possible, but also gives an opportunity to impress the patient with the need of a certain amount of rest and care in diet which of course must be continued for a long period following the bed rest, as an ambulatory form of treatment. In a study by Morrison and myself, we have shown that of 521 cases of ulcer treated by the rest method, many of which were followed up for a long time, there were 70 per cent of recoveries, as compared with 45 per cent of recoveries in

cases treated by the ambulatory method. It has become evident to us that when an ulcer patient is treated medically, he should be thoroughly treated and ambulatory treatment should if possible not be instituted at first. I am well aware of the difficulties and impossibility of carrying out this plan in all instances, but I do believe that one can expect to obtain far more satisfactory results by means of this method than by the ambulatory regime which has at least in our hands proved unsatisfactory in many instances, unless preceded by a reasonable period of bed rest. The main object therefore in advocating the rest treatment is not so much that a few weeks of bed rest will effect a cure in itself, but it will serve as a means of training and demonstrating to the patient himself the need of dietetic care as well as mental and physical relaxation over a long period of time, as a means of accomplishing an effective and permanent cure.

There can be no question but that relapses are frequently due to indiscretions following the cure when the patient is no longer under the physician's control. The patient's diet should therefore be carefully outlined and his habits regulated and when possible he should report at stated intervals for re-examination over a period of a year or more so as to determine the ultimate result of treatment.

Dr. Martin E. Rehfuss (Philadelphia): I think this is a very timely subject because it seems to fit in with the various reports that have been made before this Society in the past. I do not think we have any quarrel with the reports from Boston. They seem to agree with all the carefully tabulated reports that have been made regarding the medical treatment of ulcers.

But there was a very important thing that I did not hear in the paper and that is what was the mortality in these cases. In other words, presumably there was no mortality and if there was no mortality, then the unsuccessful cases in a sense could be given further treatment.

So far as I am concerned, I have always felt that duodenal ulcer was essentially a chronic disease. There is an acute form undoubtedly but I believe that acute form is rather an acute exacerbation of an underlying chronic lesion.

In going over these cases I have had a fairly large number of cases of duodenal ulcer. About four or five years ago I gathered all together 200 cases. I reported 100 before that. And I was more and more impressed with the fact that an individual with duodenal ulcer must live differently. We do not cure them in three weeks in the hospital. I realize that because we do a rigid *x*-ray check-up and because the lesion does not disappear from the duodenal cap. We are all agreed, apparently, that it takes somewhere around six months to two and a half years to cure an ulcer. Therefore the two-year interval is a very good one as an incidence of cure. And yet on the Continent today they are beginning to realize the essential thing in the cure of ulcer is a change in the method of living. In other words, the patient has got to accustom himself to six meals a day; he has got to live differently. You would be surprised to know what this awful catastrophy recently in the stock market has done to duodenal ulcer. The gastro-enterologists have not suffered from lack of work in the last six months I am sure and that work has largely been along this line, showing the tremendous nervous influence in ulceration and its recurrence. In three or four days we can control the symptoms but I believe that the first thing to do with a duodenal ulcer patient is to appraise him of his condition. Teach him a method of living. He ought not to smoke because there does not seem to be among the majority of people such a thing as smoking in moderation, and I can say that from personal experience.

There are two or three things I should like to call attention to:

The question of acidity. In 78 per cent of duodenal ulcer cases there is a high acidity. If we follow out the acidity of duodenal ulcer we will find the one and a half hour or one and a quarter hour point show a different series of figures than we have here.

Furthermore, I do not believe we can take a duodenal ulcer case and use an ordinary stock method. In one group of cases we can neutralize the free acid with calcium; in another with soda, bismuth and magnesia. Why, I cannot tell. But I try in difficult cases to figure out for myself what combination of circumstances will control the free acidity because the free acidity certainly has something to do with continuance of lesions.

Another question: the deformity of the duodenal cap. I believe in gall-bladder work and duodenal work we are getting to the place where we have to have roentgenographic control. The question of deformity I believe is not nearly

as great as the type of deformity. I believe the actual crater of the ulcer can be demonstrated in the cap. I frankly would much rather have a cap grossly deformed than I would one that showed a sharp niche which is more difficult to control. I am always afraid of niche rather than deformity. Furthermore, those of us who do our own fluroscopy realize the deformity of the duodenal cap takes a long time to disappear. The cap very quickly apparently smooths out in a partial way. But I do think myself it is the best criterion for ulcer healing and I do think it is the best criterion as to the stage of treatment.

Another thing is that duodenal ulcer frequently heals over with stenosis and a partially healed ulceration will frequently be just as definite an indication for surgery in an individual as in a patient who has no success whatsoever so far as symptomatology is concerned, because he is beginning to get gradual stenosis, definite retention, hypersecretory crises and vomiting. Then he will be a surgical risk.

Dr. J. L. Kantor (New York): I want to take just a minute to register a plea for the abolition of the term "peptic ulcer." I think the title "Factors Influencing Prognosis in the Medical Treatment of Peptic Ulcer" could be improved by indicating whether the ulcers discussed are gastric or duodenal or both. In the present stage of our knowledge I think we ought to distinguish between duodenal ulcers and gastric ulcers and even jejunal ulcers. Gastric ulcer is a rather rare disease; duodenal ulcer is very common. Duodenal ulcer occurs in men about nine times as often as in women. Gastric ulcer occurs approximately evenly between the two sexes as far as I know.

Dr. L. G. Cole (New York): I wish to congratulate the speakers primarily on the fact that they were discussing one particular lesion; that is, an ulcer beyond the sphincter and were not messing the discussion up with gastric ulcer.

It is evident that the first discusser prepared his paper before he heard their paper, and, therefore, assumed that they were not going to stick to the subject of duodenal ulcer, and he made his remarks evidently as intending to include both pre-pyloric and post-pyloric ulcers. I hope that if nothing else is accomplished by repeatedly harping on this subject before this Society, sooner or later, we may learn to discuss one or the other of the regions, I do not care which, and not attempt to discuss both at once, or apply the findings of one region to the problems of the other.

On the question of cap deformity and crater deformity, there is a great controversy as to which is of greater value. There is no question, however, but that a cap deformity is the essential factor which determines whether a patient has or has not an ulcer, because Akerlund, who is most enthusiastic about the diagnosis being based on the crater, finds craters in only from 60 to 75 per cent of the cases. How about the other 40 per cent, if one is depending upon the crater?

The crater deformity is a certain type of ulcer, an acute ulcer that a patient did not have when he went to bed at night but wakes up at five o'clock this morning with an ulcer and when he comes downstairs at nine o'clock, four hours after onset of symptoms, one can see that ulcer, and see it by the evidence of the crater. I would one hundred times rather have that type of crater than to have a cap deformity such as Dr. Rehfuss spoke about. So there are certain types of cap craters that are relatively no more significant than a canker in a person's mouth. The thick deep turbid crater with a rather deep hole, with a heavy ridge that is there day after day and week after week and month after month, is a more serious type of ulcer. And even that has a tendency to heal completely but its ability to heal completely and stay healed is very slight. Therefore, if one can observe that crater from time to time and see that it is diminishing and flattening, this observation becomes a valuable criterion in determining whether it is healing and the rapidity of the process of repair.

I am not nearly as enthusiastic about the disappearance of the cap deformity being a factor as perhaps some others are.

I think that when one sees a real cap deformity the patient is pretty likely to carry it to the grave, but it may not hasten the trip.

I should like to say, as to the results of medical and surgical treatment, gastric ulcers heal and stay healed, although others may form. The ulcer beyond the sphincter is a totally different thing. They are much less likely to heal and either they or cousins or brothers or sisters develop afterward to an extent of 46 per cent. I hope that we are going to find that other 4 per cent because for some period of time I have said, when I have been

asked "Do you think a postpyloric or cap ulcer ought to be treated surgically or medically?" I have said, "You are damned if you do and you are damned if you don't," meaning that the prognosis was equally bad with or without surgery. I hope that we may find the other 4 per cent to bring the evidence up to that fifty-fifty to justify my prophecy of a fifty-fifty chance for recovery.

Dr. Burrill Crohn (New York): I wanted to ask Dr. Jordan whether she takes into consideration the factor of the incidence of infection, head colds, tonsillitis, other respiratory infections as causing recurrence of ulcer. In our experience it is a very important factor in initiating recurrence. I should like to ask Dr. Jordan whether she made any studies of cigarette smoking or smoking in general upon incidence of ulcer and causes of recurrence.

Dr. Sara M. Jordan (*Closing*): I want first to explain the discrepancy between the figures which appear in the abstract in the program and the paper which we actually presented. We had a series of 851 cases of ulcer which we intended to review here as we did these cases of duodenal ulcer but we found that 66 of them had been treated with ambulatory measures (with some reluctance on our part) and we therefore did not include them in this series. Two hundred and sixty-six had not been sufficiently well followed. Eighty-four were gastric lesions and we did not wish to mess up this paper, as Dr. Cole said, with the gastric ulcer cases because we feel that although they may be identical in etiology, they certainly are a distinct form which requires a different form of treatment. Forty-three were gastrojejunal and those also fell into the class which we felt should be considered separately.

With regard to the evaluation of the results, only a few of this 46 per cent came to surgery. Many of them had one recurrence during a period of three or four or five years which lasted perhaps a week or perhaps two weeks, but the symptoms of which were so definitely felt by the patient to be the same as his original symptoms that we included them in this group showing a recurrence.

Another difficulty as we all notice I am sure in evaluating ulcer results is the fact that just when we have our group of good cases and bad cases assorted, one of the good cases may perforate or two or three of the unknown cases, hidden cases which we have not heard from for two or three years possibly because of some embarrassment due to their financial relations with us, will suddenly appear again and say they have been perfectly well during that time. So that both ways the statistics are changed even after they are compiled.

The purpose of the study was to give us some idea as to what to tell the patient when as Dr. Cole says the patient comes and asks: what shall we do with this duodenal ulcer? Will it be treated medically or surgically? We feel that now perhaps we have a little better foundation upon which to base a statement as to the prognosis. We also feel that we may perhaps in some of these cases treat them with a combined treatment, medical and surgical.

I wish to tell Dr. Rehfuss that 0.8 per cent of the patients die with medical treatment.

Dr. Cole: we also got together the surgical results of a group of cases and found that in five years 48 per cent of them came back or had a recurrence during that time so that the figures stand about equal: 46 per cent medical and 48 per cent surgical.

The deformity of the bulb I think perhaps needs a little more careful study. In our cases we have not been able to distinguish between the two types of penetrating lesion. But that penetrating type of defect was found equally often in the unsuccessful and successful group.

Regarding smoking, I always tell patients that it is my impression that we can divide our successful and unsuccessful cases into those who do smoke and those who do not. That is perhaps exaggerated but smoking does play a very large part in recurrence.

In regard to infections, we do see a relationship between injections and recurrence of ulcer symptoms, but I cannot give you the statistics. The effect of an acute attack of influenza or sinus or other respiratory infections is often seen in conjunction with a recurrence.

DIARRHEA OF UNKNOWN ORIGIN*

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IN these days of scientific medicine, it is remarkable that even the specialist who has every means of diagnosis at his command must still stand puzzled before most of his cases of diarrhea. My impression gained from reviewing records in The Mayo Clinic for 1930 was that in more than two-thirds of the cases in which diarrhea was the major complaint, there was nothing definite to explain the condition.

In order to analyze more carefully the data in this large group of cases, I reviewed the records of 100 cases of diarrhea in which the cause was indeterminate. Fortunately in some instances, the patients returned for observation, at which time it was possible to make a more positive diagnosis. Most of the patients had had treatment elsewhere for so-called colitis. The feeling at the Clinic is that the suffix "itis" should refer to inflammation and therefore the term colitis should be reserved for those cases in which actual inflammation of the colon can be demonstrated by the roentgenogram or by sigmoidoscopic examination.

In the series of 100 cases, specimens of the stools had been examined by experts for intestinal parasites and cysts; in some instances bacteriologic studies were made for *Bacillus dysenteriae* and other pathogenic organisms. Sigmoidoscopic and roentgenographic observations were made in each case. In 88 per cent of the cases, the gastric acids were tested. In every case, general examination was made to rule out systemic diseases, such as tuberculosis and hyperthyroidism. Few of these patients had lived in the tropics. Several had been treated for amebiasis. Parasites of some type were present in the stools of 31 cases. Two and often five or more stool examinations were made in almost every case. The parasites identified were: *Endamoeba coli* in 11 cases; *Endolimax nana* in 7 cases; *Giardia lamblia* in 5 cases; *Chilomastix mesnili* or *Trichomonas hominis* in 7 cases; *Endamoeba histolytica* in 2 cases, and *Embadomonas intestinalis* in one case. It might be assumed that *Giardia lamblia*, and certainly *Endamoeba histolytica*, were the causes of diarrhea in these particular cases were it not for the fact that when the parasites were removed by proper treatment, there was no improvement of the diarrhea. Obviously it is possible for persons to harbor intestinal parasites which have nothing to do with their diseases and which apparently are commensals; they may be likened to fleas, which are parasites to be sure and well worth removing, but not the cause of the symptoms. I find it difficult to agree with the statement that in a high percentage of cases[1,4] intestinal parasites may be suspected from the history. In 31 cases of the series in which the intestinal parasites did not play a part in causing the diarrhea, the histories were not different from the remainder of the cases in the series.

The general condition of the entire group of patients may be thought of as varying from the extreme of no general impairment to that of the need for immediate hospitalization. The ratio of males to females is 1:1.3, somewhat above the 1:1.1 ratio for all patients in the clinic. The ages varied from nineteen to seventy-five years, about two-thirds of the cases occurred in the decades from thirty to fifty years. The diarrhea had lasted for a few months to as long as thirty years in several cases. The diarrhea was constant in 37 per cent and intermittent in 63 per cent. The stools

* Read before the American Gastro-Enterologic Association, Atlantic City, N. J., May 4 to 5, 1931.

usually were watery, light in color and occasionally were frothy; they contained varying amounts of mucus, but no blood except that which came from the anus. Stools occurred chiefly during the day, perhaps more in the morning hours. Stools at night were not uncommon and occurred even in one case of diarrhea of neurogenic origin. The loss of weight varied from slight to almost half of the patient's original weight. In a few cases, there was no loss of weight and in some cases there was a slight gain. It is interesting to note that diarrhea may persist for months or years without demonstrable evidence of impairment other than the annoyance of frequent stools.

The treatment elsewhere in these cases was extremely varied; the two most striking procedures were the diet and irrigation of the colon. In some cases dietary restrictions were self-imposed, but usually they were prescribed. Often food essentials were deficient, especially protein. Meat seemed to be considered injurious, just as it has been in many other diseases. Not infrequently bran had been used, as well as other well-advertised preparations. Irrigation of the colon with various solutions had been done in many cases, perhaps with no particular injury in some cases but in others it was a definite factor in causing the continuance of the diarrhea. In no case was it apparent that persistent irrigation of the colon had helped to correct the trouble. Last year at the meeting of this Association, Friedenwald and Feldman reported their unfavorable results from irrigating the colon of the dog; I am inclined to believe that the colon of the human being is equally rebellious to such treatment. Seven patients had previously undergone appendectomy in the hope that it would cure the diarrhea. Two patients had had cholecystectomy and one patient an exploration on the possibility of tuberculosis of the bowel. None was benefited. When definite attacks of appendicitis or cholecystitis occur followed by diarrhea, it is reasonable to assume that there is a cause and an effect, and of course in this type of case operative procedures are justifiable.

For purposes of diagnosis and treatment, I attempted to group these patients according to their symptoms, physical conditions, and often according to their response to treatment. The attempt was discouraging, as each review of the data resulted in rearrangement. I do not feel, therefore, that the following groupings are definite but they serve as a basis on which to conduct further studies.

Neurogenic Diarrhea. In the 4 cases in this group there was no organic cause found for the diarrhea and in each case the disturbance of the bowel was definitely related to emotional strain. One patient had had attacks of diarrhea which occurred only between midnight and 1:00 A.M. Two patients had had diarrhea only during the day; another patient had had diarrhea both day and night. One patient had lost 30 pounds in weight; this was definitely related to insufficient food which the patient hoped might control the diarrhea. In such cases, one must not state too positively to the patient that nothing is wrong. A diagnosis of nervous diarrhea cannot always be easily made with any degree of certainty.

Reflex Diarrhea. In this group of 6 cases an attempt has been made to classify the type of diarrhea which is associated with symptoms of the bowel that are secondary to disease or dysfunction of some other organ. Diarrhea may be merely a symptom of disease elsewhere in the body, for the intestine is an organ of excretion as well as of absorption. In 3 cases the diarrhea followed attacks of abdominal pain suggestive of appendicitis or of cholecystitis. The removal in the clinic of these organs in 2 cases, the appendix in one case and gallbladder in the other, cured the diarrhea. One patient was advised to have cholecystectomy but refused and reported a year later that she still had diarrhea. The cardiorenal system was seriously impaired in one case, and as that improved the diarrhea improved, although diarrhea was

the patient's chief complaint on admission. One patient was relieved elsewhere of the diarrhea by removal of a remaining ovary and the uterus after medical measures at the clinic had been unavailing. The sixth patient had had diarrhea during her first pregnancy and thereafter had diarrhea with each menstrual period and occasionally between periods; this is certainly suggestive of stimulation of the bowel by the pelvic organs. Only one case of this type was noted in the series of 100 cases, but it is not uncommon to see diarrhea associated with normal menstruation.

Irritable Bowel. I am using the term irritable bowel only in cases in which the function of the bowel was irregular and apparently independent of any disease process. There were 31 cases in this group. There was no striking dietary deficiency although the diets tried had been numerous and varied. The results of examinations were within normal limits with the exception that in 7 there was an average loss of weight of 25 pounds which, however, was definitely related to faulty diets. Nineteen of the patients were men and 12 were women. Most of the patients were aged from thirty to fifty years and had been troubled with the diarrhea from one to thirty years, the majority from one to five years. Eight patients had had mild to moderately steady diarrhea, 12 had had diarrhea alternating with normal stools, and 11 had had diarrhea alternating with constipation. The factor of nervousness was usually present and yet this factor was by no means as clear-cut as in neurogenic diarrhea. The patients were not, as a whole, seriously ill, but the diarrhea interfered with their work and pleasure.

Allergic Type of Diarrhea. Most of the 18 patients in this group gave a history of some type of allergy, either direct or indirect. By indirect I mean migraine, urticaria, and hay fever. By direct, I refer to diarrhea occurring following the use of milk, chocolate, clams, buckwheat, more than 10 per cent carbohydrates, pork, carrots, corn, cabbage, fats and beans. In one instance, diarrhea culminated in an epileptic attack, and with the control of the epilepsy the diarrhea improved. Thirteen patients were women and 5 were men. Fifteen of them had had intermittent diarrhea which had lasted on an average of three to four years. The stools were usually watery with more or less mucus; 3 of the patients had diarrhea also at night. In 2 cases free hydrochloric acid was not present and its administration did not benefit the patient. Such patients were seldom anemic. Six of the group had lost an average of about 15 pounds in weight. Skin tests were disappointing in almost all instances in which they were tried. One woman who knew she was sensitive to buckwheat gave a definite skin reaction to buckwheat.

A diagnosis was made of nervous exhaustion or neurosis in many cases, which is in accord with the general feeling that most allergic phenomena occur in cases in which the patients have a hypersensitive nervous system.

Diarrhea Following Acute Infection of Unknown or Uncertain Etiology. The 7 patients in this group had suffered from acute disturbance of the bowel coincident with respiratory infection, acute tonsillitis, or acute gastrointestinal disorders, from which the diarrhea dated. It could not be determined whether the diarrhea was due to the original organism or whether the infection depleted the patient's reserve and the diarrhea developed. In all cases the diarrhea had been steady and of varying intensity. It continued for three months to eleven years after the appearance of the acute febrile disease. Striking laboratory data were absent in all cases and in only one case was loss of weight permanent, although weight was lost and gained by the others, according to the activity of the diarrhea. It is possible that culture of the stool along the lines suggested by Castellani might have proved enlightening. The stools were usually watery, with some mucus; in one case they were frothy.

Deficiency Diarrhea. In this group of 19 cases the contributing cause of the diar-

rhea, and in some instances the original cause, seemed to be due to deficient diet. Eleven of the patients were women and 8 were men; the average age was between thirty and forty. The diarrhea developed gradually and had persisted for six to twenty-five years with an average of slightly more than six years. The diarrhea was steady in 8 cases, and intermittent in 11 cases. The stools were watery, occasionally green and frothy, and tended to occur more often in the morning, often beginning at 4:00 A.M. and continuing until noon. Among the peculiar eating habits it was noted that the patient: (1) had lived on boiled milk for months because of stomach trouble; (2) had eaten very little because he was afraid food would increase the diarrhea; (3) did not like meats, fresh fruits, or fresh vegetables; (4) lived on soft foods to decrease weight; (5) acquired the habit of eating little but shredded wheat; (6) limited the dietary on his own initiative because of diabetes; (7) lived chiefly on coffee, bread and butter; (8) ate mostly white bread and beans, or (9) dieted to relieve arthritis, and so forth. In some cases striking dietary deficiency was not recorded but in these cases there was a history of long and careful dieting to control diarrhea. Loss of weight was a constant observation and varied from about 10 to as high as 80 pounds with an average of about 25 pounds. Secondary anemia was present; in some cases the hemoglobin was as low as 43 per cent. The illness of the patient depended on the extent of dietary deficiency as well as on the duration of the deficiency. In 13 cases free hydrochloric acid was not found by test meal, and the administration of hydrochloric acid seemed to be a contributing factor in controlling the diarrhea in 3 of the cases. In 3 other cases hydrochloric acid increased the diarrhea. The results of general examination were negative except for loss of weight.

Sprue-type of Diarrhea. Several of the 13 patients in this group were so ill on admission that they were placed in the hospital at once. One patient came from Texas; the remainder were from the north temperate zone. Diarrhea had persisted from one and a half to thirty years, although in the majority of cases it had persisted about five years. The ages ranged from twenty-one to seventy-five years; the majority of patients were aged from twenty to forty years. As in other groups, the diarrhea was either steady or intermittent. The stools were watery, often large and bulky, grayish, and occasionally frothy. Loss of weight of from 10 to 50 pounds occurred in all but 3 cases. A secondary type of anemia was the rule; the hemoglobin was about 50 per cent. In one case, the blood picture was similar to that of pernicious anemia. The case had been diagnosed as such elsewhere, although free hydrochloric acid was present. Repeated transfusions of blood had been of little value. The tongue was usually red and somewhat atrophic, and stomatitis was common. Several patients complained of cramps in the legs and feet. In one case *Endamoeba histolytica* was identified but antiamebic treatment did not benefit the diarrhea, although the parasite had been destroyed. In 6 cases free hydrochloric acid was absent but in only one case did its administration seem to help control the diarrhea. In both the preceding group and this group further observation may show new symptoms and lead to a different diagnosis, such as pernicious anemia.

Faulty Fat Digestion. There were 2 cases in this group. The stools were grayish-yellow, frothy, and contained macroscopic fat. One patient had lost 10 pounds, and the other had lost 60; however, their general condition was good. Diet had been adequate, although restricted at times. There was only slight anemia. Hydrochloric acid was absent in one case and its administration did not help the diarrhea. Thaysen recently reported on the problem of pancreatic diarrhea, in which he emphasized three observations on which to base a diagnosis: azotorrhea, steatorrhea, and alimentary glycosuria. Because I know of no satisfactory method for determining

pancreatic function, and because of the fact that all but complete obstruction of the pancreatic duct occurs in inflammatory or malignant disease of the head of the pancreas without diarrhea being a constant symptom, I prefer to use the term faulty fat digestion rather than pancreatic diarrhea. Although the patients in this group were not studied along these lines, yet alimentary glycosuria was not present on ordinary diet. Fat was present in the stools but the content of nitrogen in the stool was not tested.

COMMENT

Following a carefully taken history and general examination, it is the procedure in the clinic to make series of examinations of the stools on two or preferably three successive days. Experience is necessary in making the sigmoidoscopic examination in order not to diagnose proctosigmoiditis or ulceration when changes are the result of irrigations or injury from the enema tip. The roentgenogram of the colon by the barium enema is much the better means of obtaining data as to the status of the colon. Exception must be made with regard to the six-hour film for the ileocecal coil, following barium by mouth. The roentgenogram of the colon does not appear to give any positive evidence in this group. I am often asked about the significance of diverticulosis of the colon in relation to diarrhea. I believe that it seldom, if ever, plays a part. Rankin and Brown reported an incidence of 11 per cent of diarrhea in association with diverticulitis. It was not true diarrhea but usually more of rectal tenesmus with the rather frequent passages of mucus, pus and feces, due to the inflammation of the sigmoid.

A test meal is of importance in many cases. In this series of 100 cases a test meal had been given in 88. Free hydrochloric acid was present in 61. Five of the patients had been given acid without benefit; it was given to two others who thought it had helped. Of the 27 who did not have free hydrochloric acid, 6 were benefited by the use of acid; 5 of these had the steady type of diarrhea. Seventeen did not derive benefit; the effect of the acid on 4 was not recorded. This group of only 6 of 23 patients without acid who were helped by the administration of acid is too small to be of significance. In control series studied by Magath and Brown, only 10 of a group of 100 patients with achlorhydria had diarrhea of unknown origin and even in these 10 it is unlikely that all would have been benefited by acid. Emery recently reported a similar study on the low incidence of achlorhydria as a factor in diarrhea. I agree with his impression, that even when patients are benefited by hydrochloric acid, there is probably some other factor present; the low acid is merely a part of the syndrome.

The tests of skin sensitization must be considered and especially should be tried in the allergic type of diarrhea. My experience with these tests has been limited and the results as a whole have been discouraging. In all but an occasional case of allergy, the patient offered the clue to the sensitive foods. It is to be hoped that refinements of technique in this field will be evolved.

Further studies, such as a cholecystogram, roentgenograms of the stomach, investigation of foci, the metabolic rate, and so forth, are necessary in some cases.

TREATMENT

The diet is so often a contributing factor in increasing or even producing the diarrhea, and proper food is so essential to cure these patients that I shall consider diet first.

In cases of acute exacerbations or of acute diarrhea of indeterminate origin, care should be taken not to add to the patient's difficulties. In most cases the patient can get along a day or two without food, if sufficient fluids are given. Hypodermoclysis or intravenous solutions may be resorted to if necessary. Occasionally it may be advisable to clean out the bowel

with a small dose of castor oil or a saline laxative, but as a rule in these acute cases the intestinal tract has been fairly well cleaned out and a laxative adds insult to injury. After the first day or two, food should be added slowly and be of a simple, low-residue type, such as boiled rice with cream or butter, broths, crisp toast, and tea or coffee. I do not believe that boiled milk is of value in these cases. Childrey and Alvarez showed, experimentally, that milk alone is a high-residue food. The "boiled milk and bismuth" order for acute diarrhea is time-honored, and is perhaps continued from custom more than from satisfactory results.

Moro recently reported satisfactory results in the treatment of acute diarrhea of childhood by the administration of 100 to 300 gm. three times daily of the pulp of raw apples; absolutely nothing else is given for two days. This method might prove of value for adults, although I have not tried it.

A well-assorted, adequate diet, administered as rapidly as is consistent with the patient's tolerance, is the goal to be achieved for chronic diarrhea of unknown origin. It is, of course, impossible to prescribe a diet which is suitable in all cases. Far more harm is done by a too limited diet than by one too free. Many patients have been on such a restricted diet that it is absurd to think they can take care of much food at first. They must be encouraged and must not be allowed to feel that food will cause their trouble to continue. At the onset the patient may fear to eat because of former restrictions and the fear that disastrous results may ensue. One woman insisted that she could not take milk but she had no trouble with cream and milk on cereal. Another woman assured me that she could not eat toast, but could eat zwieback. Still another could not eat fruits or vegetables because of the roughage, yet had been on a diet consisting chiefly of bran cereals. One woman had been convinced that proteins and carbohydrates could not be eaten at the same time for fear the mixture would explode, yet milk had been her chief diet.

In the beginning, I suggest a low-residue diet which includes 60 to 120 gm. of meat, 15 c.c. of purée of vegetables in a milk soup, and also a meat soup with purée of vegetables. An effort is made to incorporate as many foods as seem to agree in this primary diet. The foods are gradually increased, adding slowly the stewed fruits and vegetables. Finally, raw fruits and vegetables may be added. Individual variations are, of course, necessary, especially in the presence of allergy. Occasionally it is necessary to supplement the diet with proprietary concentrates of vitamines B and D.

If digestion of fat is faulty, the diet best tolerated is usually low in fat, fairly high in protein, and rich in carbohydrate.

In cases of sprue, raw liver or its equivalent is included and gradually decreased as the patient improves. For these patients, the carbohydrates must usually be kept low as their tolerance to it is poor. One patient had a rather long siege on a diet of protein and orange juice but is finally on a full normal diet.

It would be wiser in many cases for patients to be more matter of fact about their food and less introspective.

Irrigations of the colon as a routine have little if any place in the treatment of diarrhea. The occasional use of a small, warm saline enema, preferably at bedtime, may be of aid, but its constant usage is not advisable. If the bowel is irritable, especially if diarrhea alternates with constipation, small oil retention enemas may be used temporarily.

Drugs are of uncertain value. I question the value of inert powders, as they seem in many cases merely to add to the material which must be excreted. Tincture of belladonna is also of doubtful value. In occasional cases a dramatic response may result from the use of 6 grains of emetin hydrochloride hypodermically, but in such a case I think the result must be ascribed to the specific action of emetin on an undis-

covered infection by *Endamoeba histolytica*. In the types of diarrhea considered in this paper, emetin has no effect. Organic arsenicals, as treparsol, may be worthy of trial and infrequently seem to be beneficial. The benefit is probably on a nonspecific basis.

A new product that may prove of value in some cases is 2-4-dihydroxyphenyl n-heptane (dihydranol).[8] I have tried it in the postinfectious type of diarrhea and it seemed to be of value in 2 cases. In the sprue-type of diarrhea and to a less extent in the allergic type, calcium lactate in large doses over a long period has seemed useful. In some instances, I have used it with parathyroid medication. The beneficial rôle of calcium is hard to explain. It may be along the lines suggested by Scott, who thinks parathyroid dysfunction occurs, or on the basis of altered intestinal permeability of calcium absorption and excretion, according to Snell and Habein. Tincture of iodine by mouth in doses of 10 drops after meals, well diluted, has occasionally helped and is worth bearing in mind.

Vaccine treatment in irritable and allergic conditions of the bowel has received considerable impetus by the work of Dorst and Morris. During the last year, 6 patients have been treated according to this method. An adequate diet was outlined and nonspecific drugs were usually included, such as iron citrate for the anemia and calcium lactate. Soricin, orally, was included with the vaccine treatment. In 2 cases I felt that this method had proved beneficial. In the other 4 cases in which it was used it did not seem to be beneficial. Treatment along these lines will be carried out in other cases.

In 3 cases a fairly long trial had been made elsewhere than in the clinic of vaccine prepared from an organism isolated from the patients' stools. In none was benefit obtained. In each case the incorrect diagnosis had been made of chronic ulcerative colitis and the reported isolation of Bargen's diplococcus. In 3 cases in the clinic stock vaccine of chronic ulcerative colitis was administered. In one case it was administered because the diarrhea followed tonsillectomy and it was thought that a possible focal relationship might exist, as in true ulcerative colitis; in the other 2 cases, the patients insisted on receiving this vaccine. In none of the 3 cases was the vaccine of benefit. This observation is in distinct contrast to the results obtained in ulcerative colitis in which response to specific serum and vaccine is usually definite.

My preliminary impression is not especially favorable to treatment by vaccine in most cases of indeterminate diarrhea. McCarrison's experimental work may be applied to human beings in that inadequate or deficient diet can so lower the functional perfection of the gastrointestinal tract as to impair its natural immunity to the customary organisms of the colon. Whether treatment by vaccine is the approach to restoring this resistance is a matter to be determined.

SUMMARY

A study of the treatment and diagnosis of diarrhea of indeterminate origin shows that much work remains to be done. The term colitis should be reserved solely for conditions in which there is demonstrable inflammation of the colon. At present, the term has come to be indiscriminately used and often is productive of much mental distress to patients. The types of diarrhea considered here were those occurring in this particular series of cases. Further work may decide that such groups as the faulty digestion of fat, deficiency diarrhea, and sprue may be in one large group.

Suggestions are made for the treatment of acute diarrhea, especially the type which occurs postoperatively or in conjunction with intercurrent respiratory infection.

The word diet is objectionable in view of so many widespread eccentric articles and advertisements that are now existent. The patient should be impressed with the importance of proper and adequate foods.

As a routine, colonic irrigations are condemned.

Treatment by vaccine in certain types of indeterminate diarrhea may prove of value. Further work must yet be done on this phase of the problem.

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DISCUSSION

Dr. J. L. Kantor (New York): If I understood Dr. Brown correctly, he made the point that the best way to study these cases roentgenologically was by the barium enema. The chief objection to studying the colon with the enema alone is that it is an unphysiologic procedure.

I think I showed before this society that a film taken nine hours after the administration of a barium meal gives much more information about the irritability of the intestine than the enema. So I would suggest again that that method be employed. It is simple, and can be easily incorporated in any routine.

To come back to the enema, the best way in which the enema can give information in early cases is to measure the amount necessary to fill to the ileocecal valve in a given case, and check it against a standard amount required to fill the normal colon. This gives an idea of the degree of irritability of the colon under study; otherwise you have to wait for the gross changes in outline that have been so well described by Carman and Moore in the very advanced cases.

Dr. George B. Eusterman (Rochester, Minn.): I do not imagine that there is any other condition confronting the gastro-enterologist which is so often puzzling as an obscure form of diarrhea. With respect to Doctor Kantor's remarks I will say that he is very familiar with the advantages of the progress meal as regards functional disease of the intestinal tract, but I feel quite strongly, and this feeling is shared by my roentgenologic colleagues, that deviations from the normal, even though slight, are best seen in the barium-filled colon. Probably from the standpoint of function the progress meal gives more information, in the hands of the experienced observer, but from the standpoint of detection of morphologic change we prefer the other method. As gastro-enterologists, we should be mindful of the rôle that allergy plays in the production of gastrointestinal disturbances, and particularly those of the colon. Experience has taught us to be mindful of the rôle of protein hypersensitivity in every case of persistent gastrointestinal disturbance, especially in the absence of demonstrable disease or infection. It is important that the surgeon be as cognizant of this fact as the internist, in order to avoid an unnecessary operation. This is illustrated by a recent experience of an eminent eye and ear surgeon who had run the gamut of American and European clinicians and hospitals trying to get relief from an intractable diarrhea. As the attack followed a severe emotional upset the condition was attributed to a psychoneurotic state, in the absence of other findings. However, a long period of rest failed to bring relief. Examination revealed the presence of several food proteins as direct

causative factors and with their removal from his diet there was a striking recovery within thirty-six hours. The patient has continued to remain well for the past three months. Apparently the emotional upset in this case, like pregnancies and other conditions in other cases, precipitated the allergic tendency.

Dr. Walter C. Alvarez (Rochester, Minn.). Certainly it is a brave man who is willing to admit that he cannot make a diagnosis in 3 out of 4 of the cases which he sees, and I wish to congratulate Doctor Brown on his courage and his honesty. I am delighted to hear this paper because many years ago I became impressed with my inability to learn anything about the cause of diarrhea in most of the cases seen. My only consolation was derived from Richard Cabot's confession of ignorance in his chapter on diarrhea in "Diagnostic Clinics."

I was particularly impressed by the fact that even the necropsies that I had performed in a few fatal cases of unexplained diarrhea failed to throw much or any light on the cause. I remember in one case there were scores of enlarged lymph nodes throughout the abdomen, but cultures were negative and the histologic study threw no light on the nature of the infection. In another case we found a roundworm encysted in the wall of the duodenum, possibly irritating it and keeping up the intense peristalsis. In another patient no cause could be found.

It is a curious fact that a number of patients with unexplained diarrhea have suffered with it for many years and yet have not lost weight and have not become seriously ill. I know one woman who has had as many as twenty bowel movements a day for ten years or more, and when last I saw her she was somewhat overweight and still able to keep at work. One can always, in these cases, take refuge in the thought that the diarrhea is of nervous origin, but that does not help us much.

Sometimes there is also a hereditary factor, or the patient has always had a tendency to loose bowels. I recently saw a man who confessed to me that any unusual strain brought on diarrhea, much as it did in his father. A day or two later I saw his brother who showed the same syndrome.

Another curious thing about these patients is that often their diarrhea is not much influenced either by the type of food eaten or the type of treatment administered. I have seen them take large doses of medicine, which ordinarily would put a stop to diarrhea, and yet they did not improve. In some cases of course, there may be present an enteritis of the small bowel. As yet it is almost impossible with any of our diagnostic measures to learn much about the condition of the mucous membrane in that terra incognita which lies between the third portion of the duodenum and the ileocecal sphincter.

One can think of disturbances of absorption; but unfortunately, we know almost nothing about the normal functions of absorption. The work of Hosoi and Childrey, done under my direction in Doctor Mann's Laboratory, indicates that there are striking disturbances of absorption at times, due to the giving of certain foods. For instance, when we gave cheese to a dog he not only did not digest properly on that day, but for twenty-four or forty-eight hours afterward his powers of absorption were affected deleteriously.

It is possible also that at times the disturbance may be due to the removal of normal inhibition. Thus, if in rabbits one cuts the vagus or splanchnic nerves, or both sets, the animal commonly dies of diarrhea and inanition. The nerves seem to serve as "brakes" for the bowel.

There may also be disturbances in the water-absorbing power of the colon. I can remember a girl who was troubled with one of these long-continued, harmless diarrheas, and in whom it could be seen with the *x*-ray that the feces solidified normally in the transverse and descending colon. The curious fact was that when the solid feces reached the sigmoid flexure and the rectum they began to liquify again. Something seemed to have gone wrong with the mucous membrane of the rectum which caused it to excrete water into the bowel.

In some of these cases of unexplained diarrhea one can work a spectacular cure by injecting hypodermically a little typhoid vaccine. Fortunately, it seems to work best in just those cases in which nothing else will give relief. In other cases it is well, even when one cannot find amebae, to give a course of twelve tablets of treparsol. If there is no improvement, one can then be fairly certain that the diarrhea is not amebic in origin.

Dr. T. R. Brown (Baltimore): I agree with Dr. Brown in regard to the question of the unreliability of skin tests. Blackfor and I quite independently a few years ago carried out a long series of skin tests by the older methods, and we both came quite independently to the conclusion that in regard to picking out diets it was disappointing although, it was rather helpful in a certain group of cases in which the troubles were associated with various skin manifestations, eczema, erythema, urticaria.

I do think perhaps not enough stress has been laid on psychogenic and neurogenic factors in these cases and quite a few cases that have their origin in shock or nervous upset. We often think of the habit of constipation; we never think of the habit of diarrhea. Perhaps we ought to think of it in the same category. When we see how many people without structural change develop chronic constipation, is it not conceivable that quite the same thing may occur in regard to diarrhea in which we may have disturbance of this delicate balance for controlling peristalsis which spells healthy or normal evacuation. Is it not true that a certain number of cases represent the same habit factor which had its origin in something past, of which the habit has never been broken by appropriate treatment?

In one group of cases, so-called deficient fat cases, sprue-like cases, I have been helped by pancreatic studies. I think determinations from stool studies are more accurate if properly done with extreme, meticulous care. I think the cases are excessively interesting.

Last of all I want to call attention to the fact a number of cases are unquestionably missed because of the fact there is trouble in finding the causative factor. It is surprising how many cases come to autopsy in which the *Endamoeba histolytica* had not been discovered but was found then.

I have had 2 cases recently. One patient had no history of previous dysentery, had gone through several diagnostic clinics and was regarded as a case of nervous diarrhea. And yet finally the parasite was found and he is getting relief from specific treatment. Another case was one in which there was acute amebic infection five years ago and diarrhea lasting since that time in which the organism had never been found.

In that connection I want to mention again the difficulty, but also the tremendous benefit which is obtained from sigmoidoscopic study.

We must think of the possibility of diarrhea representing habit, representing psychic shock, representing unrecognized organic cause.

Dr. Sara M. Jordan (Boston): I would like to ask Dr. Brown in how many cases he found that catharsis and colonic irritations were not only not helpful but might possibly have been part of the cause of the condition, especially in the so-called irritable colon.

I would also like to say in our experience both the barium meal and the barium enema have been of value. The nine-hour picture especially, but sometimes the six-hour picture, shows the rapidity with which the barium passes along. And that seems to me a very important point in the diagnosis. The barium enema is helpful not only in the determination of the amount of material required to fill the colon but the rapidity with which it passes in. It is also of importance to determine the caliber of the colon as it passes over toward the cecum and also the distress which it causes the patient. We found that the normal colons do not react with distress to the reception of the barium, and that the barium passes in a very definite time over to the cecum, usually between two and four minutes. Also that the caliber is of a standard size; whereas in the irritable colon it is either very much diminished or very much too large.

Dr. Warren T. Vaughan (Richmond, Va.): Dr. Brown has brought out the observation that the skin tests are often negative, as I attempted to bring out in my paper. I think probably all of you recall Dr. Thomas R. Brown's paper which came out several years ago, on the food factor in migraine. He also observed that one frequently obtains what one might call false negative sensitization reactions.

Of course there are several possible reasons for this: First, our methods of preparation of the extracts are in the last analysis pretty crude. We do not know exactly what we have. I think in Dr. Thomas Brown's paper he mentioned chocolate. I know in my own experience we very infrequently get a positive reaction to chocolate and yet chocolate is a frequent offender.

The other possibility and I think this often happens, is that the reacting tissue is

limited to the intestinal tract and there are no reacting bodies in the skin. It is possible that with better methods of preparation of allergenic test substances we may, as time goes on, get a higher proportion of truly positive skin reactions.

Of course the elimination diet is not new, any more than allergy is new. Hurst, many years ago, in his book on constipation, discussing colitis, especially mucous colitis, brought out the close analogy to asthma with muscle spasm and catarrhal secretion, eosinophiles in this secretion. He remarked on the close similarity to asthma, but did not draw the analogy any further. He described a very simple elimination diet in that all he did was start his patients on milk and as they improved, added one food at a time. And in essence that was a trial diet or elimination diet.

I spoke yesterday of the extremely interesting case of Dr. Alvarez in which cheese was found to be the causative factor, not by keeping a food diary alone, but by keeping a record of the daily events of the patient's experience. Cheese is quite an interesting factor. There are many kinds of cheese. Of course Roquefort cheese is made from sheep's milk; Giedeost, a Dutch cheese, is made from goat's milk. Most cheeses are made from cow's milk, but they vary because the taste of cheese depends upon the mold growing in it, and each variety of cheese has been ripened with a different type of mold. So really we are dealing with different foods in different types of cheeses.

I would also like to say that Dr. Alvarez, so far as I know, was the first man who started the more modern work on the elimination diet.

Dr. Philip W. Brown (*Closing*): I left out a paragraph containing a point which was emphasized very nicely by Dr. Brown and Dr. Alvarez. All of these patients without exception, irrespective of stool examination, were given a therapeutic trial of emetine and treparsol and those cases that responded to the use of emetine and treparsol we have dropped out of this group because we do not consider them indeterminate diarrheas.

THE DIAGNOSIS OF JAUNDICE

VALUE OF CLINICAL AND LABORATORY DATA*

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WHEN a patient with jaundice presents himself, certain questions arise: What has happened to turn the bile into his blood? Is there an obstruction and can it be relieved? Will the trouble clear up spontaneously or will a surgical procedure be necessary? If an operation is performed, what is likely to be found and what can be done? What are the dangers of this operation and can anything be done to obviate them? What does the future hold for the patient?

There are three principal ways in which jaundice develops: (1) from production of more bilirubin than the liver can excrete; (2) from obstructive lesions occurring in the biliary tract, or (3) from some functional derangement of the polygonal hepatic cell, interfering with excretion of bilirubin. On this basis, McNee has classified jaundice as of hemolytic, obstructive, or toxic and infectious (hepatic) origin. At the clinic, we have found this a satisfactory working classification. Each of these groups of cases presents a different therapeutic problem and hence a quick classification of any case of jaundice into one of these types is desirable. This is especially true when it is recalled that obstructive lesions are those most frequently encountered, and that if unrelieved they lead to much injury to the biliary passages and hepatic parenchyma.

LABORATORY DATA

Although the differentiation of jaundice is and should continue to be based largely on clinical criteria, laboratory procedures are useful, and McVicar and Fitts have suggested the following as a working procedure: (1) determination of whether the reaction of jaundiced serum to the van den Bergh reagent is direct or indirect; (2) determination of the height and behavior of the curve of serum pigment as plotted from results of the van den Bergh test or from the icterus index; (3) determination of the quantity of bile reaching the intestine, as recovered by siphonage of the duodenal content, and (4) determination of the presence or absence of pain and of its character when present. With these data at hand, a working diagnosis can usually be reached. If an anatomic diagnosis cannot be made positively, the case usually can be classified as surgical or nonsurgical.

There is evidence in the literature of considerable difference of opinion in regard to some of the functional tests of the liver. The liver has multiple functions, a large reserve capacity, and an ability to regenerate rapidly after severe injury. From a practical standpoint, in jaundiced patients, the clinician will employ any one or more of the proposed tests if he finds that they will supply him with useful data in regard to the following: (1) to aid in determining whether the jaundice is hemolytic, obstructive, or hepatic or in determining if there is more than one type of jaundice present; (2) to give some idea of whether the reserve capacity of the liver is sufficient to enable the patient to stand surgical procedures when indicated and to recover, especially when obstruction is present; (3) to give some idea as to the prognosis in hepatic jaundice, and (4) to determine the most favorable time for operation, or indication for any particular type of treatment. I do not propose even to list the various tests of hepatic function,

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but I wish to present the results of observations of certain tests.

Van den Bergh Tests. In the experience of our section the qualitative and quantitative van den Bergh tests have given more definite and useful data than any of the others. The determination of the character and amount of bilirubin in the serum gives a much more accurate idea of the type of the icterus, its severity, and its fluctuations than does examination of the urine and feces or study of the color of the skin. By means of the van den Bergh reaction, hemolytic jaundice, in which an indirect reaction is usually obtained, can be distinguished from obstructive or hepatic jaundice. An occasional case of hemolytic jaundice is seen in which the van den Bergh reaction is delayed direct or indirect, suggesting possibly some disturbance of the parenchymal hepatic cells, but the larger part of the pigment present gives an indirect reaction. The character of the reaction does not aid in distinguishing obstructive from hepatic jaundice, or in determining whether there is an hepatic element present in the case with obstruction. A measure of the retention of bilirubin in the blood serum, however, does give some assistance. In hemolytic jaundice it is extremely rare for the reading to be more than 8 or 10 mg. in each 100 c.c. of serum. In the hepatic group the value for retention of pigment may be extremely high and seems to be proportionate to the severity of the disease. Table 1 gives the values for serum bilirubin in a group of 224 cases of obstructive jaundice and in 100 cases of hepatic jaundice. More than 70 per cent of the cases in which the disturbance is due to stone or stricture of the common bile duct have a value for serum bilirubin of less than 10 mg. in each 100 c.c., the highest readings for bilirubin occur in cases of malignant obstruction and hepatic icterus, and a value for serum bilirubin of more than 30 mg. in each 100 c.c. is presumptive evidence of hepatic origin of the jaundice. There is also much evidence to suggest that in benign, incomplete obstruction, persistent elevation of bilirubin of more than 15 mg. is strong evidence of an associated intrahepatic element in the production of the icterus.

Table 1

Serum Bilirubin in Various Types of Obstructive Jaundice

Serum Bilirubin, Mg. in Each 100 C.c.	Stone in Common Bile Duct (102 Cases)		Stricture of the Common Bile Duct (46 Cases)		Carcinoma of Pancreas (36 Cases)		Carcinoma of Gall Bladder and Ducts (16 Cases)		Cholecystitis with Stones (24 Cases)		Intrahepatic Jaundice (100 Cases)	
	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
1 to 5	42	41	20	43.5	4	11	1	6	8	33.0	18	18
6 to 10	30	29	14	30.5	5	14	3	19	6	25.0	27	27
11 to 15	21	21	7	15.0	8	22	4	25	5	21.0	18	18
16 to 20	8	8	3	7.0	12	33	8	50	2	8.5	11	11
21 to 25	1	1	1	2.0	5	14	..	..	2	8.5	9	9
26 to 30	..	..	1	2.0	1	3	..	..	1	4.0	4	4
31 to 35	..	..	..	....	..	..	..	..	..	....	4	4
36 to 40	..	..	..	....	1	3	..	..	..	....	4	4
41 to 45	..	..	..	....	..	..	..	..	..	....	3	3
46 to 50	..	..	..	....	..	..	..	..	..	....	2	2

Groups of cases of stone in the common bile duct, cicatricial stricture, carcinoma of the pancreas, and carcinoma of the gall bladder or bile ducts, in which there was evidence of complete obstruction, were selected. It was surprising to find that the bilirubinemia averaged practically the same

in the four groups; that is, from 16 to 18 mg. for each 100 c.c. It is difficult to explain the finding of much higher readings

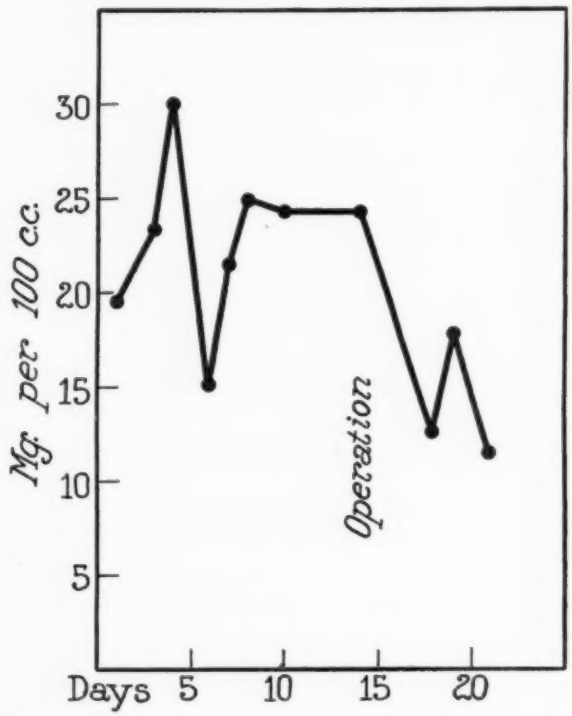

Fig. 1. Concentration of serum bilirubin showing marked fluctuation preoperatively.

than this average in these cases if the icterus is considered to be due solely to obstruction. It is equally as difficult to explain the cases in which the readings are much lower than the average. In some of the latter, associated anemia or long duration of the icterus may be a factor, but in many cases these are insufficient reasons for the low readings.

A single determination of the concentration of bilirubin in the serum is helpful in giving an accurate gauge of the degree of icterus and classifying its type, but more information can be obtained by following the curve from day to day, for significant changes may not be observable clinically, and important hints in regard to the clinical course, diagnosis, therapeutic indications or contraindications, and prognosis, may be obtained. In the obstructive group, declining bilirubinemia indicates a favorable course and greater safety for surgical procedures, whereas a rising curve argues for delay in surgical intervention. An adjustment of some kind is taking place, and it is much safer to delay operation until equilibrium is established and the curve remains at a definite level.

Sudden fluctuations in the amount of bilirubin in the serum suggest that there is a little less obstruction, and this usually means the presence of a cause of intermittent obstruction, such as calculus. The following case illustrates this point and also the probable hepatic factor associated with an obstructive lesion.

A woman, aged sixty-one years, registered January 27, 1931. In May and in September, 1930, she had had moderately severe attacks of "acute indigestion," requiring opiates for relief. In December a similar attack had occurred, followed by jaundice. This had now been present for a month, and there had been loss of weight of 30 lb. Aside from the icterus which was of a brilliant yellow type, nothing significant was found on general examination. There was considerable anemia. The percentage of hemoglobin was 50 and erythrocytes numbered 3,790,000 in each cubic millimeter of blood. On duodenal drainage evidence of free flow of bile was obtained. The concentration of serum bilirubin was 19.7 mg. in each 100 c.c. on admission, but the rapid fluctuation illustrated in Figure 1 suggested intermittent obstruction. This was confirmed by subsequent occurrence of a Charcot type of fever. The high retention of bilirubin, in spite of the free flow of bile into the duodenum, the anemia, and the brilliant yellow type of icterus suggested an associated hepatic element in the production of the icterus. At operation the gall bladder and cystic duct were full of stones; the common bile duct was much dilated and contained two stones, lying loosely in the ampullar region. The liver, grossly, appeared in fairly good condition. Death due to complicating bronchopneumonia prevented further observation of the degree of hepatic involvement or of its response to relief of the obstruction.

It has already been mentioned that bilirubinemia of 30 mg. or more is presumptive evidence of the hepatic origin of the jaundice. In the presence of bile entering the intestine, and in the absence of pain,

this is especially true, and under these conditions, values for serum bilirubin much lower than 30 mg., even as low as 15 mg., are very suggestive of hepatic jaundice. The intensity of the bilrubinemia is usually suggestive of the severity of the hepatic injury, although it does not necessarily parallel the clinical symptoms. For example, a patient whose serum bilirubin measures 50 mg. in each 100 c.c. may rapidly recover, whereas one with 20 mg. in each 100 c.c. may have a condition which is progressing to yellow atrophy. In Table I it will be noted that 26 per cent of the patients with hepatic jaundice had a value for serum bilirubin of more than 20 mg. and 13 per cent of more than 30 mg. It is difficult to explain the apparent discrepancy between this marked bilirubinemia seen in cases of hepatic jaundice, in which the ducts are patent and that occurring in cases of obstructive jaundice, even when the occlusion is complete.

The behavior of the curve of bilirubin in hepatic jaundice also offers some diagnostic and prognostic assistance. A persisting high value, with little fluctuation, suggests extensive injury to the liver. A rapidly falling curve is usually a good omen whereas a slowly falling curve indicates more serious injury.

Excretion of Dye. The rate of disappearance from the blood of dyes which have a selective property, so that they are excreted through the liver, has attained deserving popularity in recent years. In cases in which patients are not jaundiced, the dye tests give valuable information. This is especially true in the differential diagnosis of ascites, or in determining the efficiency of the liver in such conditions as Banti's disease when splenectomy is being considered. In certain types of hemolytic icterus, some information concerning hepatic function may be gained, and it is also demonstrated that in cases of obstructive and hepatic jaundice, when the icterus has about cleared, there is still evidence of some injury to the parenchymal hepatic cell as demonstrated by these tests. Generally speaking, however, among jaundiced patients these tests seldom give information that cannot be obtained by simpler methods.

Coagulation Time and Sedimentation Rate of Erythrocytes. The hemorrhagic tendency in jaundice leads to the complication that is chiefly responsible for the surgical risk. In most instances this tendency is detectable by measurement of the coagulation time, and by the presence of purpura or of slow oozing from incised surfaces. Occasionally, in severe cases, there may be spontaneous bleeding from supposedly intact tissues or, rarely, evidence of thrombocytopenia. Snell, Vanzant, and Judd recently summarized knowledge of this hemorrhagic tendency. The sedimentation rate has been shown to be increased in jaundice, but Burke has been unable to demonstrate any relationship of this to the type of jaundice or to any hemorrhagic tendency. It is sufficient to say here that frequent determination of the coagulation time is an important laboratory procedure in cases of jaundice, remembering, however, that the tendency to bleeding may not always be demonstrable by this means, that it may occur in cycles, and that this natural variation should be remembered in selecting the time for necessary surgical intervention and in evaluating the results of treatment.

Urobilin and Urobilinogen. Determination of the concentration of urobilin and urobilinogen in the urine has been advocated as a means of differentiating types of icterus. From a theoretical standpoint, it might appear valuable in determining complete obstruction of the bile ducts, but in the cases in which assistance in differential diagnosis is most needed, that is, in distinguishing between cases of hepatic jaundice and those due to partial obstruction, it can be of little if any, assistance. I have not noted any assistance from demonstration of urobilin or urobilinogen in the urine from either a diagnostic or prognostic standpoint. McVicar

and Fitts summarized their impression of the significance of this test.

Lactic Acid and Sulphates in the Blood. Study of the lactic acid in the blood has also been suggested as a test for hepatic cases, the results were lower than normal. In others, there was a slight increase, but it was not sufficiently great or frequent to be of diagnostic value. There appeared to be no correlation with the degree of

TABLE II

CHOLESTEROL, CHOLESTEROL ESTER AND LECITHIN IN CASES OF JAUNDICE

Case	Preoperative			Postoperative			Degree of Obstruction	Diagnosis and Comment
	Mg. in Each 100 C.c. Plasma							
	Cholesterol	Cholesterol Ester	Lecithin	Cholesterol	Cholesterol Ester	Lecithin		
1	715	379	1041	667	287	1248	Complete	Carcinoma of hepatic ducts; exploration
2	230	94	544	287	137	578	Complete	Obstructive jaundice, probably carcinoma
3	...	...	....	184	151	215	Almost complete	Carcinoma of pancreas; cholecystogastrostomy
4	287	105	568	145	...	378	Almost complete	Carcinoma of pancreas with metastasis to liver; exploration
5	387	216	568	321	170	355	Moderate	Carcinoma of pancreas with metastasis to liver; exploration
6	574	277	1041	188	142	284	Moderate	Carcinoma of right hepatic duct; removal
7	...	...	....	347	185	544	Moderate	Carcinoma of gall bladder; exploration
8	113	49	297	...	...	...	Moderate	Carcinoma of pancreas; cholecystogastrostomy
9	...	...	....	146	75	272	Mild	Carcinoma of pancreas
10	...	...	....	74	37	139	Slight	Carcinoma of pancreas
11	185	89	347	189	152	320	Marked	Cholecystitis with stones; obstruction of common bile duct
12	196	101	380	...	...	...	Moderate	Stone in common bile duct removed
13	297	175	478	...	...	...	Moderate	Stones in gall bladder and obstruction of common bile duct
14	185	150	223	158	104	223	Mild	Stone in common bile duct; T-tube
15	565	277	1156	350	228	473	Complete	Stone in common bile duct removed; T-tube
16	340	282	347	189	167	208	Mild	Stone in common bile duct removed; T-tube
17	62	54	178	85	64	164	Slight	Stone in common bile duct; external biliary fistula
18	208	98	355	260	216	297	Marked	Stricture; excision and reconstruction of common bile duct
19	595	379	1248	245	163	290	Marked	Stricture; hepaticoduodenostomy; pregnancy
20	422	175	568	211	89	312	Complete	Stricture; reconstruction over T-tube
21	...	...	....	383	219	696	Marked	Stricture and biliary cirrhosis postoperatively
22	318	143	478	...	...	...	Marked	Stricture; hepaticoduodenostomy
23	154	79	290	...	...	...	Mild	Stricture; biliary fistula; suppurative hepatitis
24	...	...	....	337	139	595	Moderate	Stricture postoperatively; T-tube
25	206	144	320	155	103	233	Mild	Stricture; external fistula; transplantation
26	238	175	328	...	...	...	Slight	Stricture; duodenal fistula; hepaticoduodenostomy
27	354	204	594	358	173	544	Complete	Obstruction of the common bile duct; pancreatic cyst; jaundice unrelieved
28	241	131	390	...	...	...	Marked	Hepatitis; cleared in three weeks
29	135	56	201	...	...	...	Moderate	Postarsphenamine jaundice
30	137	49	215	...	...	...	None	Acute yellow atrophy from cinchophen
31	238	136	328	...	...	...	Slight	Biliary cirrhosis
32	378	278	520	...	...	...	Mild	Residual hepatitis with jaundice; secondary biliary cirrhosis
33	219	189	338	...	...	...	Slight	Secondary biliary cirrhosis
34	175	143	205	...	...	...	Mild	Atrophic cirrhosis (alcoholic) with ascites
35	105	75	195	...	...	...	None	Cirrhosis with ascites
36	128	84	189	...	...	...	None	Cirrhosis with syphilis

insufficiency. Wakefield and Greene reported their experiences with this test in a series of 20 cases from The Mayo Clinic. Their opinion is that, with the method used, the resting lactic acid content of the blood gave no information. The usual normal values obtained by the method employed ranged between 10 and 15 mg. in each 100 c.c. In several of their retention of bilirubin. Wakefield and Greene also reported their studies of the sulphate fraction of the blood. They found a reduction in the ethereal or conjugated sulphates in 11 of 26 cases. These 11 patients were seriously ill. More recent work, however, on the method for inorganic and conjugated sulphates, has shown that many normal persons do not

have measurable quantities of conjugated sulphates in the blood, indicating that their absence from the blood does not necessarily mean hepatic injury. It has been found further, that some conjugated sulphates may occur in the urine in the absence of any in the blood, but the amount as compared to the total content of sulphates is lower than the usual 10 per cent. Further work is necessary on the sulphate content of both urine and blood in normal and pathologic states.

was elevated. Among the 9 cases with normal values, there were 6 in which postoperative determinations were made and these were also normal. In these 6 cases there was only slight icterus, except in 1 case in which there was marked hepatitis and a concentration of serum bilirubin of 18.6 mg. Among the 16 cases in which the amount of fat in the blood was elevated preoperatively were 6 in which the values were normal postoperatively, 6 in which there was decided decline, 3 in which there

TABLE III

CHOLESTEROL, LECITHIN, TOTAL FATTY ACIDS AND TOTAL LIPOIDS IN CASES OF JAUNDICE

Case	Serum Bilirubin Mg. in Each 100 C.c.		Preoperative				Postoperative				Degree of Obstruction	Diagnosis and Comment
			Mg. in Each 100 C.c. Plasma									
	Preoperative	Post-operative	Cholesterol	Lecithin	Total Fatty Acids	Total Lipoids	Cholesterol	Lecithin	Total Fatty Acids	Total Lipoids		
37	2.2	1.5	160	300	340	500	142	230	370	512	None	Stone in common bile duct
38	7.1	4.3	294	358	653	947	184	270	373	557	None	Stone in common bile duct
39	7.9	3.1	260	280	519	779	107	195	918	1025	Partial	Stone in common bile duct
40	4.5	1.8	387	644	781	1168	125	250	1036	1061	Partial	Stone in common bile duct
41	21.0	10.0	194	496	880	1074	158	410	774	902	Complete	Cholecystitis with stones; compression of common bile duct
42	18.7	7.9	238	338	647	885	185	356	702	887	Partial	Stone in common bile duct; hepatitis; necropsy
43	23.0	11.5	173	356	813	996	128	338	1862	1990	Partial	Stone in common bile duct; hepatitis; death
44	7.9	3.0	746	1136	1967	2713	151	269	455	606	Complete	Stricture of common bile duct
45	8.8	1.7	450	624	1049	1449	336	328	699	1035	Complete	Stricture of common bile duct
46	5.5	2.0	208	267	387	595	196	285	335	531	Complete	Carcinoma of pancreas; external biliary fistula
47	13.8	2.3	617	832	1589	2207	324	312	509	833	Almost complete	Carcinoma of pancreas
48	20.3	....	340	558	965	1315	....	....	....	....	Complete	Carcinoma of gall bladder; exploration

Blood Fat. Although the liver has much to do with metabolism of fat (Tables II and III), the full details are not yet worked out. We have determined the partition of fat of the blood in 48 cases of jaundice due to a variety of conditions. At first it was thought that marked elevation of the amount of fat in the blood might aid in distinguishing obstructive types of lesions from other types. On further observation, however, this has not been found true. In 25 cases in which operative relief of the obstruction was undertaken, there were 9 in which the amount of fat in the blood before operation was normal, and 16 in which it was no change, and 1 in which there was further elevation. There were 3 other cases in which determinations were not made preoperatively and in which postoperative values were normal. Among the 3 cases in which there was no change after operation, the jaundice was not relieved in one, the elevation of the blood fats was only slightly more than normal in another, and in the third there was marked hepatitis associated with calculi of the common bile duct, and the icterus did not clear postoperatively. In the case in which the values for blood fat were elevated after relief of the obstruction, there also was extensive hepatitis associated with chole-

docholithiasis. There were 17 other cases in which no operation, or only exploration, was undertaken. In the 8 cases in which there was obstruction, there was elevation of the concentration of blood fats. The values for blood fats were elevated in 4 of the remaining 9 cases of hepatic jaundice. No correlation was demonstrable between the degree of elevation of values for blood fat and the lesion producing the jaundice. In general, in the cases in which there was marked elevation of blood fats there was marked biliary obstruction, but in many cases in which there was marked obstruction, also, there were normal or nearly normal values for blood fats.

Sugar Tolerance Tests. The important relationship of the liver to metabolism of carbohydrate has long been recognized, and evidences of disturbed glycogenic activity have long been sought in hepatic disorders. Particular attention has been paid to studies of tolerance to carbohydrate. Glucose, fructose, and galactose have been the main sugars studied. Although the liver is definitely concerned in metabolism of carbohydrate, it must be remembered that many other factors are concerned, and interpretation of results of tolerance tests must be made with great caution. Greene and his associates have reported their experience in the clinic with the use of the fructose tolerance test in obstructive jaundice in carcinoma of the liver and bile ducts, in certain diseases of the hematopoietic system, and in various types of syphilis of the liver. Although positive tests were obtained, it was with great irregularity. There was the additional difficulty of eliminating associated pancreatic disease and other factors. They questioned the clinical usefulness of the test.

Table IV gives the results of determination of the tolerance to fructose in cases of jaundice of hepatic origin. The criteria of Tallerman were accepted in determining any lowering of tolerance. Cases 49 to 55 were acute, and were of the nature of catarrhal jaundice; Cases 56 and 57 were chronic cases of jaundice of undetermined origin. Two of the patients with the acute type of jaundice had lowered tolerance; one of them also has diabetes, and the other had very deep jaundice (serum bilirubin 41.2 mg. in each 100 c.c.) of two weeks' duration. In no instance was the value for fasting blood sugar abnormal. Further work with this test was not carried out because of negative results.

TABLE IV

FRUCTOSE TOLERANCE TEST

Case	Serum Bilirubin, Mg. in Each 100 C.c.	Results in Terms of Glucose, Mg. in Each 100 C.c.				Result of Test†	Comment
		Fasting	After 100 Gm. Fructose				
			1 Hour	2 Hours	Change*		
49	41.2	78	135	107	54	Positive	Jaundice for two weeks
50	24.2	87	294	275	507	Positive	Diabetes
51	2.9	86	107	109	23	Negative	
52	17.3	84	105	84	21	Negative	
53	1.1	90	89	88	1	Negative	Icterus absent
54	1.9	93	114	105	21	Negative	Icterus absent
55	3.6	93	126	85	33	Positive	Pernicious anemia with hepatic icterus
56	20.5	92	121	112	29	Negative	Exploration
57	7.8	93	112	96	19	Negative	Icterus for three and a half years

* Difference between value fasting and highest value after administration of fructose.

† Change of more than 30 or rise above 135 = positive.

We also have used the galactose tolerance test in jaundice and hepatic conditions, and although definite changes in tolerance occur, we do not feel that the test is sufficiently specific to warrant stating that a case is of obstructive or hepatic jaundice, or that operation is or is not indicated.

Blood Guanidine. Minot and Cutler have found that guanidine is retained in the blood of dogs that are poisoned with carbon tetrachloride. High intake of carbohydrate and calcium produced marked increase in tolerance to the drug, and relief from symptoms of intoxication. The inference is that possibly in cases of hepatic disease there might be retention of guanidine. We have determined by Pfiffner and Meyer's method the guanidine content of the blood in a small series of cases of hepatic disease, but to date have obtained only normal results. Possibly in cases of more acute intoxication or degeneration there may be some increase in guanidine. However, in such cases it is necessary to exclude any associated renal involvement.

Patency of Bile Ducts. Duodenal intubation is used more than formerly because it gives more definite information concerning the amount of bile entering the intestine than does examination of the feces. Patency of the ducts seldom enters into the question of diagnosis if jaundice is of the hemolytic type. If jaundice is of purely hepatic origin, bile always can be demonstrated to have entered the intestine, although in certain stages of acute, severe types of hepatic jaundice there may be temporary suppression of excretion of bile. Pathologically in cases of hemolytic and hepatic jaundice, there is no question of obstruction of the larger ducts. In cases of obstructive jaundice, determination of the patency of the biliary tract is an important aid in diagnosis. Table v gives an analysis of a group of cases in this respect. Although other groups of cases may give percentages which vary somewhat from these, it is felt that these represent approximations which are satisfactory in general. It will be noted that there is evidence of patency of bile ducts in a high proportion of the cases of stone and the reverse in the cases of malignancy. Cicatricial stricture occupies an intermediate position. Although it cannot be claimed that patency or complete occlusion is in itself diagnostic, yet the degree of patency, taken in consideration with other facts, aids materially in arriving at a diagnosis, and is of value in indicating therapeutic procedure.

Table v

Patency of Biliary Passages

	Partially Patent		Not Patent	
	Cases	Per Cent	Cases	Per Cent
55 cases of stone in common bile duct.....	50	91	5	9
31 cases of stricture of common bile duct.....	25	80	6	20
26 cases of carcinoma of pancreas.....	8	31	18	69
13 cases of carcinoma of gall bladder and ducts.	3	23	10	77

Clinical Data

Pain is seen chiefly in obstructive jaundice. It is extremely rare in hemolytic or hepatic jaundice, although occasionally it occurs and may be due to complications. I reviewed recently 275 cases of jaundice, in which operation or necropsy was performed, with regard to the incidence and character of pain. Among 104 cases of stone in the common bile duct, there was colic associated with the onset of icterus in 80; in 19 the onset was painless. Among 49 cases of benign stricture, colic occurred in 22. In 38 cases of pancreatic neoplasm, colic occurred in 5, and icterus had its onset painlessly in 19. In 38 miscellaneous cases of cholangeitis, hepatitis, cirrhosis, and so forth, colic was present in 12, and there was a painless onset in 21. Atypical pain of various types occurred in all groups.

Colic is the most typical pain in disease of the biliary tract, and when associated

with jaundice strongly suggests stone in the common bile duct. However, in the presence of stone pain may be absent, or it may be replaced by milder equivalents. Pain may occur in other conditions, such as cholecystitis with or without stones, stricture of the common bile duct, cholangeitis, malignancy of the pancreas or the biliary tract, or in some cases of primary hepatic disease.

In distinguishing cases due to stricture from cases due to stone in the common bile duct, when operation has been performed previously, difficulty is also encountered. The patient with stone is usually free from symptoms after operation much longer than the patient with stricture. Among the cases due to stone, the average interval, in the cases reviewed, was three years and eight months. Jaundice occurs at a longer interval after operation in cases of stone than in cases of stricture unless there is persisting jaundice or biliary fistula. Immediate jaundice or persisting fistula suggests stricture. Strictures are accompanied by colicky pain much less frequently than stones. Stricture occurs as a rule only after cholecystectomy.

Cases in which pain is absent offer greatest difficulty in differential diagnosis, but if the history, results of general examination, and laboratory data are taken into consideration, a satisfactory conclusion usually can be reached. If patients are young, painless icterus is usually hepatic in origin, especially if there is evidence of an epidemic. In later years, painless icterus may be associated with palpable gall bladder, enlarged nodular liver, or other evidences of malignancy which aid in diagnosis. Painless jaundice coming on shortly after cholecystectomy suggests stricture. In some cases a definite diagnosis cannot be made, and if the patient is in good general condition and the icterus shows no signs of clearing in a reasonable time, exploration must be considered. In the group of 275 cases studied there were 107 cases in which onset of icterus was painless. These cases were due to benign stricture, pancreatic enlargement that was malignant in most cases, carcinoma of the bile passages, hepatic disease, or stone of the common bile duct.

Other signs and symptoms are frequently mentioned in differential diagnosis, especially the presence of pruritus, whether or not the gall bladder is palpable, the size and consistence of the liver, the presence of diarrhea, and loss of weight. The cause of pruritus in jaundice is unknown. It is likely to be present as often in benign as in malignant disease, and as often in hepatic jaundice as in obstructive jaundice. In 71 cases of stone in the common bile duct pruritus was present in 60 per cent, in 20 cases of stricture of the common bile duct it was present in 95 per cent, and in 26 cases of carcinoma of the pancreas it was present in 75 per cent. In one group of cases of hepatic jaundice that was studied, pruritus was present in more than 90 per cent of the cases. In the individual case it is thus evident that the presence or absence of pruritus does not assist in differential diagnosis. A palpably distended gall bladder may be present in a variety of conditions, such as carcinoma of the pancreas, carcinoma of the gall bladder or ducts, or benign obstruction of the cystic duct. It is most frequently encountered in carcinoma of the pancreas. However, in our experience the frequency with which it can be palpated is much lower than one would expect from figures obtained from textbooks or postmortem reports. In a series of cases of carcinoma of the pancreas that was studied, the gall bladder was palpably distended in approximately 60 per cent of the cases.

The size and consistence of the liver are even more variable from the standpoint of diagnostic value. The presence of a liver of normal size does not exclude a cirrhotic or metastatic process.

SUMMARY

Although much study from a clinical and laboratory standpoint has been de-

voted recently to jaundice and hepatic diseases, the differential diagnosis is and should continue to be based essentially on clinical data. The presence or absence of pain and its character when present is the most important single fact in such differentiation. Laboratory procedures have given new impetus to study of these cases, have changed methods of practice to some extent, and have introduced new conceptions of the mechanism of jaundice. Thus, duodenal drainage to determine the amount of bile entering the intestine is used more frequently because they give more definite information than examination of the feces and urine. The reaction of the serum to the van den Bergh test, and the height and contour of the curve of bilirubin give a much more accurate idea of the type of the icterus, its severity, and its fluctuations than does observation of the color of the skin or examination of the urine and feces. We feel that the van den Bergh test is one of the most useful of the various tests that have been advocated in the study of jaundice. The coagulation time of the blood is also a valuable procedure, but must also be coupled with clinical observation of the patient.

The conception has developed that all jaundice is not obstructive in cause, but that jaundice may also be of hepatic or hemolytic origin. Although the majority of cases are probably distinctly of one type, yet in practice cases are seen in which the icterus originates in more than one way. Thus, the cases of hemolytic jaundice may have an associated hepatic or obstructive element or the cases of obstructive jaundice may have an associated hepatic element. At present there is not any specific test for distinguishing between hepatic jaundice and obstructive jaundice if the obstruction is partial. The need for such a test is especially great when obstruction has developed without the accompaniment of pain.

The mechanism of the icterus in hepatic jaundice is not understood. The classification of the group is unsatisfactory. Although some forms of jaundice, such as that due to chloroform, have largely disappeared, other forms have appeared since the introduction of the arsphenamine and cinchophen drugs. Precautions in the use of these drugs are constantly necessary.

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THE PSYCHIATRIC ASPECTS OF GASTROENTEROLOGY*

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I HAVE prepared a paper in which I aimed to lead the physician who is almost exclusively taught to study parts of the organism and their functions to take an interest also in the total-function of the person.

After the papers on various widely disparate facts, nerves, allergy and the constitution, I thought I would rather try to formulate in as objective a way as I can what would be helpful for the physician in dealing with the personality functions or "mental factors" and the consideration of the relation between part-function and total-function of the patient.

I must confess that the discussion has gone into divergent detail in some respects far beyond what I planned to say on the principles of dependable correlations. We have been confronted largely with constitutional differences.

The main interest that activates me in the discussion of gastro-enterological patients is probably somewhat biased. I am not particularly interested in data concerning which I have to accept the fact that the dice have already been cast and that the life is practically nothing but the dance of factors largely settled by heredity and constitution that cannot be affected without highly specialized efforts. The principal interest that I have in a discussion with practitioners with regard to personality study and the relation between personality reaction and part-reaction is, as I feel after hearing these discussions, very definitely in the direction of more obviously accessible and simpler problems.

I have a feeling that we cannot discuss as profitably the constitutional make-ups of unusually involved and fate-determined nature as we might discuss the question of the rôle of the so-called mental factor in the simpler, more easily manageable conditions. Nevertheless I must say that I am keenly interested in and stimulated by the discussions that have preceded. I do, however, feel that it might be wise to keep rather closely to what is within the reach of every physician, although it naturally is also important to know what is possible to attain in the more difficult problems of modification of behavior patterns.

Allow me, then, to present, instead of a formal paper, some ex tempore remarks directly suggested by the present discussion but supplementing it as indicated. I should like to explain why and how I should like to urge the physician to think and work with frank attention to the personality functions, and particularly those which are pliable and within the reach of the practitioner. Instead of speaking of a psychiatric aspect I should rather speak of the personality-reactions to be considered in addition to the local or part-reactions.

It is somewhat unfortunate that we are perhaps very strongly led to carry off from the modern discussion of the personality-reactions the anecdotal and more or less startling facts that one gets out of the very detailed study of the cases in the literature. One is apt to think in terms of topics of life that can be discussed in their proper setting but that cannot always be made the issue of direct questions to the advantage of either patient or physician. The consequence is that a good many patients, who after all have to be treated as plain human beings, as possibly sensitive personalities, become very definitely startled, if not offended, by the questioning by the practitioner who thinks too hastily of what may be the upshot of long and careful studies of the sex con-

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stitution and the sex functions and a good many of those things that the individual cannot readily change, but that cannot profitably be probed into in a hurry, as little as it is advisable to poke hastily into wounds with a probe.

For the physician it is of tremendous importance to realize that if he wants to get at facts, he has to give the patient an opportunity to speak without too much of a tendency to shock by searching for finished pictures derived from highly specialized systems such as those of psychoanalysis.

I have no antagonism to the following up of such correlations as the ones that Dr. Draper has particularly emphasized. I think they are of considerable plausibility and they are fundamentally quite interesting and they will be infinitely more interesting to me when I shall be able to derive certain principles by which to help the average individual to make more adequate adjustments.

Instead of leaving the impression that in most cases we have to probe at once into the sex life when we suspect "mental factors" to be playing a rôle, I should emphasize the fact that after all practically every fundamental function can take a lead in the personality constitution, in this sense, that, for instance, the gastrointestinal function may have just as much of a tendency to express the personality and *to be* the personality as the sex function can in its way be the main representative of "the personality" in certain situations and in certain periods of life. I should say that the gastrointestinal receptive, digestive and eliminative functions can become that which expresses, and leads the government of, the person for certain periods of the day or throughout life as a dominant and leading concern. It is in our present cultural situation not so prominent. At the same time I think it worth while to recognize that so much of our actual existence is given over to the intake of food, digestion, and reaction thereto and to the elimination, especially in certain individuals, that it will form a matter of concern, a matter that offers possibilities of becoming dominant and of playing a very definite rôle when anything goes wrong.

It is quite interesting that from the psychoanalytical side intake and elimination and the reactions thereto have been practically identified with sex preoccupations or associations and undoubtedly there are a good many individuals in whom combinations of that sort are quite prominent. The question then arises: What do we know of gastrointestinal functions assuming the rôle of personality-reactions at the expense of both the structure and the function of the parts under a leading preoccupation?

I like to present the facts as zones or spheres and types of implication which have to be understood as mutual concerns and neither by argument nor by exhortation. The gastro-enterologist finds that a patient comes to him with certain functional and even structural disturbances, and he is confronted with the question: Is the malfunction of the stomach or colon structural-functional, due to some local disorder, or is it essentially derangement due to collisions with other particular components either of the gastrointestinal structure and functions or some other organ complexes or of the personality functions? We get local disturbances which depend upon structure, for instance, in the presence of any irritating content of the stomach and the reaction of the mucous membrane thereto. We may then get a spreading of the reaction of the stomach upon the bowel activity, as an extension of the situation. Similarly the stomach may be upset incidentally to what is a disturbance elsewhere in the intestinal tract. Or an existing enterological disturbance may have to include even more to be intelligible. We may deal with an involvement of the thyroid functions, or a disorder of the adrenals, vitamine or metabolism deficits and things like that. We may find, in a more or less autonomous

form, a neurological involvement of the vagosympathetic balance. Then we may pass to questions of the taste of food, i.e., actually into the field where more or less conscious processes become participants, until we get into those functions where the same activity, also seen autonomously or reflexly as activity of special parts, becomes quite definitely part of the *personality reaction*, i.e., consciously emotional, or actually more or less voluntary functioning. And as soon as we get into that field we have to take into consideration that we are dealing with factors in which we may have to deal with a need of a personality-history with possibly a long and special accumulation of life experiences and reactions.

We may deal with a very direct structural or local irritation in vomiting, or with vomiting that comes from neural reflexes as in seasickness, through an overflow of labyrinthine activity; we might next add the vomiting phases belonging to an even larger circle of facts, namely, the pregnancy vomiting. In still another case we have to confront ourselves with the facts of vomiting from a possibly *fancied* pregnancy, i.e., a personality situation to be understood and digested without ridicule, offense or exhortation. In other words, we get the same type of reaction, i.e., the vomiting, in a number of combinations in which we come to the question whether we are dealing with a non-mental integration or whether we are working with a mentally integrated activity. The conscious or more or less conscious processes are in their way just as real and objective facts and processes to the individual as any other, and indeed facts and situations concerning which the student and physician should acquire as adequate training as about infections, poisons, and functional clashings or inhibitions. Hence the traditional prejudice that the "mental facts" might belong to an unreal world obnoxious to the physician might well be transformed into a realization that they form a simple and direct continuity with the "non-mental" facts.

There then presents itself the question of a practical understanding of what disturbances of the gastrointestinal tract can be part of emotional states, of complex emotional and topical experiences, autosuggestion and things of that sort, which are mentally integrated processes in contrast to merely physiologically conceived processes, calling for a knowledge of personality functions and personality implications.

What is possible in these directions is a matter of experience and the best opportunity we have of determining this experimentally probably is with hypnosis, because there we have in our possession a method of inducing also less conscious experiences practically dissociated from the general trend, but as clearly active or potent as definitely conscious ones. It should no longer appear strange that with self-suggestion or suggestion by others it is possible to produce structural alterations, since, in the end, all function must be function of structure, as was shown long before Pavlov. It is worth remembering that under suggestion it is possible to bring about such a fundamentally physiological and "physical" process as menstruation obtainable on suggestion on a definitely given hour. The same will hold for the motility and tonus and secretion and circulation of other viscera.

Now if in the light of that sort of condition we size up the susceptibilities of organs in a number of directions or settings, we get in a position where we can make comparison between what occurs in the disturbances that are likely to be attributable to specific non-mental conditions and factors in the organs and those in which we have suspicions that we are dealing with so-called "nervous" affection and personality implications. Evidently the fact that the "nervous" disorder is carried on by neural processes does not make it "non-mental." The question is whether associative links and especially specific emotionally active situations can be demonstrated, and whether they influence

the occurrence or can make the occurrence disappear. The mentally integrated functions are also "physical," but we find them to be part of experiences best studied for what they are and mean to the patient and for ways that bring out mutually intelligible situations.

If a physician attempts to get at facts of this type, he is apt to ask too hastily about things which the patient either guards very carefully and is sensitive about or might not know about, i.e., would have in a form which does not rise in response to a blunt question. If I ask you, "What emotional tendencies are you subject to?" I think most of you would probably for a moment feel blank; you would probably be reminded more readily of emotional things if asked what things are apt to get a rise out of you, and then there gradually would be a looming-up of emotional situations that might be telling also in actual complaints.

So in the study of our patients it is tremendously important to be sensitized to the *facts* and to give opportunities to speak, but without precipitating antagonism by such questions as: Have you or any of your people had hysteria? Or nervousness? That might at once appear as an objectionable charge. One has got to prepare the ground on which the individual can really find an incentive to seek aid instead of blocking the way for further discussion. If a physician bluntly asks questions about certain things which the patient has to deny to save his or her face, something arises which may militate absolutely against the formation of a mutual understanding and may bring about a multiplication rather than a reduction of things that are disturbing.

What I have illustrated as the types of settings and situations to be thought of in vomiting holds also for diarrhea, constipation, the fluctuations of appetite. We only have to think of the biological susceptibility of an animal that is taken from the free life into captivity and a process of domestication where in one way or another the animal reacts with a loss of interest in food and that at times to the point of starvation. We get equivalents of that sort of thing in depressions in the human being. Nostalgia used to produce very serious pictures in recruits in the armies where now we get the scare-reactions of "shell shock." Today with the ease of changes and the consequent habituation those same tendencies, where they still exist, are very easily smoothed over so that it is rather difficult to get at any very telling and conscious admissions of such emotional factors. But we have to learn to sensitize ourselves to situations that call out the equivalent of those emotional effects which entail the disruption of the gastric and intestinal functions. That in depressions constipation plays a very important rôle, we all realize. Whether we shall succeed in explaining that either neurologically or in any very satisfying way from a general biological point of view is perhaps very remote. It still will be part of depression. What we do want to know is the lines along which we can see variations, fluctuations, and then possibilities of inducing the variations to occur at our will and to the advantage of the patient. Sometimes a part-adjustment will help; but if the disorder is *essentially* psychobiological, i.e., an implication of the person, it may have to be met on that ground.

Very often colitis has factors of a definite emotional character; and there we are apt to deal with individuals that do give us the picture of a great deal of self-concern and self-analysis, something to be taken into account. It is our task then to reconstruct the real situation in a way intelligible and acceptable to the patient and inviting a desire to correct the combinations and not only the local reaction.

There has been a great deal of controversy about the importance of gastrointestinal disturbances in the production of mental disorders. I suppose it is wisest to weigh carefully how much is part-disturbance and how much is general disturbance. I have not been able to make up my mind

to look upon those things in a categorical way in terms of the "either—or"; it is always wisest to pay attention to the whole range of factors that may be found playing a rôle and that can be reached.

The great difficulty at the present time lies in the fact that the whole of medical education still tends to throw the weight on the things that we know relatively little about before we enter the medical school. And under that influence there is perhaps a cloud formed over the things which we all are supposed to have lived with and to know. And it is for that reason that it is rather difficult for the medical student either to keep, or to resuscitate, the interest in the problems of emotional life and the conflicts that are apt to occur and the relations, let us say, to the cardiac functions or the gastrointestinal functions and so on. The student is apt to be put under obligation to think and speak of "nerves" and not of the obvious or at any rate important facts as found and as known as calling for adjustment. I do, however, hope that it will be possible to get very much more of a practical training along these lines, particularly if a practice can be established of having somebody who is primarily interested in the personality-reactions become a liaison officer in the correlation of the gastrointestinal clinic and the psychiatric clinic. George Stevenson has made an attempt in that direction at the Cornell Clinic. I cannot help but feel that a great deal can be done to get the student into the habit of at any rate familiarizing himself with the socializable disturbances or irregularities that can be reached by a regulation of life. That a good many of us prefer occupation treatment to mere talking is due to the fact that after all we have not yet as excellent control over the things that form the fancy and the thought life of the individual; whereas we look upon performance and activity as the actual functioning and the test of the working of the individual's drives and life. There, in connection with activities, in connection with the behavior outside and within, and with the planning of constructive behavior, we are doing something that creates at least an opening which is very much to be desired, particularly where one does not have at one's disposal that unlimited time which is required when you tap those parts of the individual's life that are more or less unstable in practically all of us.

I do think that the intimate understanding of the more superficial disturbances of equanimity and of conduct ought to be put as emphatically before the medical student as the more specialistic formulations, which after all ought not to be used as a ready-made code in terms of complexes and mechanisms but which ought to be accepted only where careful study and actual demonstration, and not suggestion by examination, are sure to be had.

I repeat that there are two ways before the psychopathologist. The one way may be taken where he has unlimited time for investigation and where he can allow himself to go into all the features, tap all the points that may or may not ultimately be the true picture of the person's maladjustments and difficulties and opportunities for mending. But the other is that of training one's self to evaluate the assets and opportunities as well as the handicaps and complaints and not to do harm by abrupt and blocking questions. That the questions of plan of treatment ought to be taken up with due consideration of the emotional factors is perfectly obvious, but obvious as it is, it is very little heeded. Sometimes one faces the interesting question whether the desire for operation and the subsequent pleasure of talking of one's operation is not as good a placebo as some other placebos that the practitioner is likely to use. And one has to recognize that one should not necessarily kick at the physician who is using one or another guess in the direction of operative interference and things like that. Nevertheless, I think it is sad that we still do get patients who arrive practically eviscerated, for a

last trial, which very often ought to have been the first—namely, that of getting the life adjustment within the range of socialized health offered while it can be fully used.

That we have a great problem in the patients who become chronic, who apparently do not want to get well, is another issue, viz., the question of invalidism. And there I must say I have seen a variety of procedures, not by any means always the adjustments by so-called deep psychology, but the organization of life with the help of the imagination of a physician where the imagination of the patient may be lacking. After all, we have plenty of experience that this works, and it certainly does work very much more extensively than is the case in the average treatment without training, and seems to figure in the minds of those who are too (I do not want to say physically-minded, because according to my conception all human functioning is also physical functioning) exclusively part-minded, with attention only on a narrow focus.

Where one does find personality conditions, one naturally also runs up against family problems, and the unwillingness of the public to allow us to take a patient under treatment against his or her will and things of that sort. It is certainly an important thing to carry to the student the idea that, with the raising of the bed "against enteroptosis" and that sort of thing, one may be helping largely by suggestion of considerable benefit with some individuals; but, after all, the organization of the average life is apt to be of a great deal of value and importance as well.

The reason why I have not gone more into the specialized issues, the issues of so-called psychoanalysis and particularly the special types of reduction to one or another system is this: in the first place, after all, there are far more disturbances of the gastrointestinal tract that are personality-functions and personality-determined, than it would be possible to treat with more problematic and protracted types of intensive psychotherapeutic treatment. And I do think that from the point of view of public pathology, the pathology (i. e., the ideas about disease) of the average American individual, it will be something of a relief and something of a help if those things which can be handled with the simple socialized types of regulation and personality adjustment are treated with the simplest methods.

ACUTE PANCREATITIS

ACUTE HEMORRHAGIC PANCREATIC NECROSIS*

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SINCE the first publication on this subject in 1889 by Fitz who made a most complete study of all available cases which at that time could be recognized as coming under this heading, many cases have been reported, but not enough to make the condition a common one. Then came the publication of the general and minute pathology by A. S. Warthin in 1898 in which he reports a careful study of changes in the viscera. The pancreas in his case was much enlarged, weighing 320 gm. It was about three times the normal size, abundantly infiltrated with fat, showing the same necrosis as the omentum and mesentery. The organ was hemorrhagic throughout, the blood from a large hemorrhage having formed a clotted mass to the left of the head of the pancreas.

Klebs in 1870 was first to associate hemorrhage of the pancreas with the severe symptoms which we now recognize as the syndrome of hemorrhage into and necrosis of the pancreas.

The papers of Fitz, Warthin, Klebs and Friedreich give us a fine working knowledge of the disease. There have been many suggestions as to the causes leading up to the sudden onset of symptoms and there is yet much room for additional work in both predisposing and exciting etiology. There has been some considerable discussion which suggests that under this heading of acute pancreatitis we are dealing with two different conditions both clinically and etiologically. One has been called acute hemorrhagic pancreatic necrosis (Opie), and the other acute suppurative pancreatitis. Under the former would come the traumatic variety, both external and internal trauma, those cases due to the blocking of the duct by stone in the ampulla of Vater or other causes of a backward flow of bile and distention of the gland under pressure, also apoplexy of the organ (Opie) due to a break in a pancreatic vessel.

Friedreich in 1875 presented a more or less complete picture of acute pancreatitis suggesting two varieties: the hemorrhagic, which may result in gangrene, and the suppurative type which was found in the infectious diseases in which abscesses were located in and about the pancreas. There are also, no doubt, many cases of bacterial invasion of the pancreas in mild form which give rise to abdominal symptoms of digestive disturbance, the source of which is unrecognized.

As to the gangrenous type of the disease: There seems to be no doubt that back flow of bile into the duct of Wirsung, whether contaminated by pathogenic organisms or not, will under pressure up to and above 1000 mm.[1] produce acute hemorrhagic pancreatitis or necrosis and gangrene of the gland. It has also been shown that tauracolate of soda of the strength found in the natural bile will when introduced into the duct under pressure bring about the same condition. Injection of artificial gastric juice into the pancreatic duct of animals and the use of other irritating chemicals in the same way caused hemorrhage into the pancreas and death in a few days. The omentum and mesentery showed fat necrosis, so that it appears to require not an infective agent or a susceptible host but

[1] Mann, F. C., and Giordano, A. S. *Arch. Surg.*, 6: 1–30, 1923.

* Read before the American Gastro-Enterological Association, Atlantic City, N. J., May 4 and 5, 1931.

merely overdistention under pressure by bile or other fluid, a backward pressure distending the gland so as to bring about some slight solution of continuity in the blood vessels.

Apoplexy of the gland has been observed as the cause in a small percentage of cases studied post mortem.

Trauma as instanced in the injury of the gland by the kick of a horse, the passing over the body of the wheel of a wagon, crushing the pancreas against the vertebra, and gunshot wounds of the glands are recognized causes.

In many instances, disease of the pancreas is secondary to diseases of the biliary tract and acute pancreatitis is not an exception. Through obstruction of the duct of Wirsung by gallstones or other obstruction increasing pressure within the gland, through ascending inflammation, through the extension of adjacent abscesses, through direct extension of inflammation and as a source of hematogenous infection, the biliary tract plays a part in the etiology of acute pancreatitis.

The work of Mark Kaufman[1] seems to successfully refute the opinion of Deaver and others as to the lymphatic theory of pancreatitis, i.e. the extension through the lymphatics of infection from the gall bladder and bile ducts to the pancreas producing acute pancreatitis. He suggests that clinical and anatomical data rather than experimental evidence resulted in the belief that the lymphatic route was a source of pancreatic infection but Kaufman's experimental work leaves no doubt as to the faultiness of the lymphatic theory.

Arnsperger admits his failure to so produce the disease while he believes it is clinically possible.

The pancreatitis of infection will not as a rule show fat necrosis while the necrotic pancreas is accompanied by extensive fat necrosis in omentum, mesentery and other tissues. The association of fat necrosis with acute pancreatitis seems to be a point in differential diagnosis between hemorrhagic necrosis of the pancreas and acute bacterial inflammation of the pancreas of the suppurative type which is not commonly accompanied by fat necrosis. Where abscess is found with fat necrosis it might lead to the conclusion that the abscess was secondary to hemorrhagic necrosis and not a part of a bacterial suppurative pancreatitis.

Infection of hematogenous origin cannot be dismissed with the same conclusion as that of the lymphatic route. Since we believe that no part of the body is free from exposure to acute inflammation of hematogenous origin this cause must be given careful consideration. It seems, therefore, more likely that one variety of suppurative pancreatitis might be attributed to infection of hematogenous origin. Some of the cases which have a gradual onset, with forerunning symptoms having been observed, followed by increasing pain and suppuration rather than hemorrhage and gangrene, I believe, will be found to be due to infection through the circulation. Consideration of the several possible causes of pancreatic abscess suggests separating these cases of the suppurative type into different groups: first, those caused by extending inflammation; second, those of hematogenous origin; third, those that are a part of an infectious disease. (This gland is subject to inflammation quite similar to parotitis and inflammation of it does occur in mumps, and may be followed by abscess.) Fourth, it may be the result of ascending inflammation; fifth, it may follow hemorrhagic necrosis, the onset being sudden with the intense pain and other characteristic symptoms, but in most cases has its origin in infection without the violent symptoms of the necrotic type of pancreatic disease.

Peripancreatitis may exist as an extension from perigastritis or duodenitis or other adjacent inflammations. This was suggested by Chiari who reported a case of round ulcer of the stomach with extending inflammation to the pancreas with abscess.

[1] Kaufman, M. *Surg. Gynec. Obst.*, 44: 15–22, Jan. 1927.

The extension of inflammation by contact or spread directly through the tissues is not to be confused with the suggestion that it may extend through lymphatic channels from the gall bladder to the pancreas.

DIAGNOSIS AND SYMPTOMS

The usual symptoms of the gangrenous type of pancreatitis are: intense pain, vomiting, profuse sweating, at times swelling and tenderness, no increase in temperature (sometimes it is subnormal). The skin is a pale dusky color. Shock, collapse and death usually occur on the second to the fourth day or even within a few hours. At operation or postmortem there is evidence of fat necrosis.

The general appearance is that of great toxemia. Doberauor produced such symptoms by transplanting experimental necrotic pancreases within the peritoneal caviy of normal animals.

The pain may be above or below the umbilicus, usually above. There is usually normal or subnormal temperature. The pulse is as a rule rapid and collapse precedes death which frequently occurs in from two to four days from the onset. Vomiting follows soon after pain begins and may be frequent and persistent.

The recognition of this condition is at all times difficult and unless we have in mind this infrequent pancreatic tragedy, the usual painful pathological conditions of the upper abdomen are likely to be considered instead of this greater catastrophe. The very severity of the attack with its shock, agonizing pain, profuse sweating and the recognition of the patient's state as one of extreme gravity far beyond the common acute pathological conditions of the pancreatic region are the keys to the diagnosis.

The matter of most importance in diagnosis is not to differentiate before operation but to recognize when an acute surgical abdomen exists and not to delay operation when it is known that a matter of hours may be of such tremendous importance in saving the life of the patient. It is a fortunate situation when the patient can be seen almost at the onset of the pain. Case 1 here reported was seen within a few minutes of the onset and was given a half grain of morphine sulphate and sent at once to the hospital where the abdomen was opened without any unnecessary delay.

There is a group of cases of the necrotic type which gives the following general history: A man in robust health in middle life inclined to over nourishment, carrying a little more than the normal amount of fat, having had no previous symptoms, after a full meal is suddenly the victim of a severe and agonizing pain in the upper abdomen. The prostration, shock and general severity of the attack should lead to at least a tentative diagnosis of acute pancreatitis.

TREATMENT

The treatment of all forms of acute pancreatitis is, I believe, surgical. In the hemorrhagic necrotic type surgical interference should be immediate.

In the case of more gradual onset with inflammation and abscess some delay might not be disastrous but from our somewhat limited experience we believe that the interest of the patient will be best protected by very early operation.

Deaver questions the advisability of operation in some cases of profound shock but in fulminating cases he advises immediate surgical intervention.

CASE HISTORY

H.B. male, aged forty.

Chief Complaint: Severe pain in the upper abdomen.

Analysis: For the past two years the patient has had indefinite pains in the abdomen from time to time. His friends state that during this time he has had occasional attacks of abdominal pain after meals. He claims only belching and fullness after meals but says he is a heavy eater. About a month ago the patient had a somewhat more severe attack of pain but it cleared up after the vomiting of food.

The present condition started suddenly at about 3 P.M. on May 20, 1930 while the patient was at work at his desk. He was attacked by a severe abdominal pain and went at once to a drug store for medication but the condition only became worse. Gastric lavage and vomiting did not relieve the pain which was still growing worse. The patient was becoming weak and was sweating profusely. He was given a half grain of morphine and sent at once to the hospital for operation.

Past Medical History: There had been vague abdominal pains occasionally for one and one-half years which cleared up after medication. No serious illnesses.

Past Surgical History: No major operations.

Family History: Wife is living. Father and mother are both dead, the former of glaucoma and the latter of a streptococcic sore throat. No acid fast or malignant history.

Social History: The patient works as an accountant. He sleeps eight to nine hours daily. He drinks coffee, liquor and smokes very little.

Physical Examination: The patient is a well-developed, well-nourished white adult male lying in bed apparently suffering from acute, very severe, surgical abdomen. Head and Neck. The head is well shaped. Eyes react to light and distance, movement of eyes is normal. Nose and ears are normal. Teeth are in fair condition. Tonsils are in good condition. Thyroid is small.

Chest: The chest is moving but little and there is present the grunting type of respiration, characteristic of an abdominal catastrophe.

Cardiovascular: The heart rate and rhythm are slow and regular. Pulse shows no irregularities. Heart is within normal limits.

Abdomen is boardlike in rigidity. Peristalsis is present but slightly. Nothing can be felt. The patient is writhing and groaning with intense abdominal distress.

Reflexes: Hypo-active.

Adenopathy: Negative.

Blood sugar 140.

Impression: Acute pancreatitis.

Final Diagnosis: Acute hemorrhagic pancreatic necrosis.

Surgeon's Report: Aged forty, admitted May 20, 1930. The patient has always been a big eater. He is exceptionally well nourished. He has had indefinite pain in his epigastrium at times for two years. Has had much fullness and belching after foods at times. One hour before admission the patient was suddenly seized with acute severe pain in his epigastrium. He was nauseated and his pain was not relieved by a fourth of a grain of morphine. He consulted Dr. Jones and was brought to the hospital immediately. On admission his symptoms were those of acute pancreatitis or perforated duodenal ulcer. His pain was agonizing. His abdomen was tense and distended. Peristalsis was slow. Temperature 96°F., pulse 90, respiration 24. Laparotomy was performed on admission. Gas anesthesia was used. On opening the peritoneum, I found blood-stained serum under the liver around the gall bladder and duodenum. The stomach, duodenum and gall bladder showed no evidence of disease. The head of the pancreas was hemorrhagic and edematous. The body of the pancreas was firm and lobulated. I did not search the lower half of the abdomen. I opened the peritoneum over the head and right half of the pancreas and drained with two large cigarette drains and a rubber tube. The spots of fat necrosis, so commonly seen in acute pancreatitis, were not in evidence, perhaps because of the earliness with which this patient came to operation. After operation pancreatic fluid drained and there was quite a little sloughing of the tissues around the drains (due to action of the pancreatic fluid). After the drains were removed his incision closed promptly. I saw the patient about two weeks ago and he claims excellent health.

The point that I would make with reference to this acute hemorrhagic pancreatic necrosis is to urge operation as early as possible. I believe this patient's life was saved because I saw him within twenty minutes from the time the pain began.

DISCUSSION

Dr. Julius Friedenwald (Baltimore): I would like to call attention to 4 cases of acute pancreatitis reported by Doctor Thomas S. Cullen and myself. In our publication we followed the classification of Fitz as to the three forms: hemorrhagic, gangrenous and suppurative. These really represent various stages of the same process which begins as the acute hemorrhagic lesion.

The first case was in a diabetic patient with gallstones and acute nephritis. The patient

was a female sixty-seven years of age. She was suddenly attacked with pain in the umbilical region, followed by continuous vomiting and was in a state of extreme shock. There was marked abdominal distention, rigidity and extreme tenderness, and a leucocyte count of 26,000. At operation a quart of bloody fluid was found in the abdomen and fat necrosis was extensive. The gall bladder contained a few small stones. The patient died a few hours following operation.

The second case also occurred in a patient affected with cholelithiasis. The patient, a female of twenty-four years, had had numerous attacks of typical gallstone colic. She had been pregnant and had gone through a normal confinement two weeks prior to her entrance into the hospital. She was suddenly taken with acute abdominal pain in the region of the gall bladder with vomiting and obstinate constipation. On entering, she was in a state of shock with rapid pulse and subnormal temperature. The abdomen was distended and rigid. A diagnosis of cholelithiasis with perforation was made and immediate operation advised. On entering the abdomen a serous fluid was encountered and milky patches of fat necrosis noted in the omentum and peritoneum. The gall bladder was enlarged and contained from 30 to 40 mulberry-like stones; the gall bladder was drained and the patient made a satisfactory recovery.

The third case was also in a patient with cholelithiasis. She was a female of sixty years who had been affected for many years with attacks of indigestion occurring at irregular intervals following meals. She was suddenly seized with violent epigastric pain, nausea and vomiting. She entered the hospital in a state of shock. The abdomen moved but slightly in inspiration and the walls were rigid and there was extreme tenderness under the right costal arch and in the epigastrium. The leucocyte count was 22,700. On opening of the abdomen a turbid, reddish fluid escaped containing many small flakes. The omentum contained numerous small areas of fat necrosis. The gall bladder was drained and contained one large stone and several small ones. The patient had a stormy convalescence but was discharged after six weeks in good condition.

The fourth case was one of acute pancreatitis with gallstones and subsequent abscess formation. This occurred in a female thirty-four years of age; who had complained of a mild gnawing pain in the upper abdomen at irregular intervals; which recently had become more frequent and intense, requiring morphia for relief. She was admitted to the hospital with extreme abdominal pain and the diagnosis of cholelithiasis made. On opening the abdomen small whitish areas were noted scattered over the surface of the omentum. The pancreas was found much enlarged and the fat presented numerous areas of necrosis. The gall bladder was drained and three stones removed. Following operation, the patient was in extreme shock and the outlook seemed poor. The patient, however, recovered from the immediate effect of the operation, but the temperature began to rise about the third week and she vomited continuously. She lost ground, could not retain food, became weak and drained profusely. On the twenty-first day a definite mass could be detected about the lower third of the gall bladder incision. This was found to be the wall of an abscess cavity which was drained and finally healed and the patient made a good recovery. Of our four cases, all were affected with gallstones and three of the four recovered.

Dr. Arthur C. Clasen (Kansas City Mo.): Those of us who have seen many cases of acute hemorrhagic pancreatitis in the experimental animal are amazed at the rapidity in which death takes place, namely: six to twenty-four hours in spite of all therapeutic measures both surgical and medical. The cause of this exodus makes one speculate somewhat.

Generally there is present a large amount of sanguinous fluid in the peritoneum often without visible fat necrosis or gross liver or kidney change; only a portion of the pancreas may show evidence of the large hemorrhage or a well-formed clot without evidence of recent bleeding; yet the remaining portion of the pancreas may appear perfectly normal. Death in these animals probably is not due to the profound anemia produced or to the external pancreatic secretion. We have noted definite changes in the blood chemistry of these animals; some showed marked increase in the urea, non-protein nitrogen and carbon dioxide with a definite fall in the blood chlorides and sugar resembling those changes noted in high intestinal obstruction as discussed by Doctors Orr and Hayden; again other cases show

(*Continued on page 522*)

UNUSUAL AND COMMON FORMS OF BACTERIAL DYSENTERY OBSERVED IN THE SOUTH*

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IN a seven year survey of the dysentery cases due to bacteria occurring in the extreme Southern section of the United States, we have had the opportunity to study clinically and bacteriologically approximately 100 cases. As a result of these investigations there are sufficient data to confirm the findings expressed by other Southern observers and the previous reports of ourselves. That is, bacillary dysentery is endemic and apparently on the increase in some states. We are also enabled to make the first report from the South of cases of bacillary dysentery due to the bacillus of Duval and the second in the States since the discovery of the organism in 1904. Another purpose of this communication is to include descriptions of cases that represent certain unusual types of bacterial dysentery encountered in the present study.

First with brief references to the incidence of acute and chronic bacillary dysentery, we agree with Boyd,[1] who in 1921 expressed the belief that bacillary dysentery is too often overlooked. That writer made a plea for concerted effort in recognizing this form of dysentery. Boyd reported 2 cases of the disease occurring in Texas and showed that the Flexner and Hiss-Y bacilli were present and that contamination was taking place through the medium of the carrier.

In 1926,[2] a small group of cases, originating in Louisiana and due to the Flexner bacillus, was reported by one of us.

Ashworth, Upchurch and Straus[3] in 1926 and Higgins[4] in 1928 described bacillary dysentery in Virginia. Tht latter expressed the thought that the disease is apparently on the increase in that State.

DIAGNOSIS

An acute bacterial dysentery, which is in the great majority of instances one of the bacillary group, is initiated by sudden and generalized abdominal cramps with a rise in temperature. Several hours and sometimes one or two days may elapse before the onset of diarrhea. The individual may show marked signs of toxemia, especially preceding the bowel eliminations. Following the passage of retained feces, the stools are characterized by bloody mucus which on microscopic examination contains much pus but no *Amoeba histolytica* except in the mixed infection. There is more difficulty in the recognition of the chronic and low grade state of facillary dysentery. The chronic case may or may not have had its onset in the acute symptoms. There may be only an occasional diarrhea and at times an alternating constipation. The stools are soft to watery, containing mucus and are rarely blood tinged. In the temperate climes, the Flexner bacillus infection is predominate and the chronic cases are mild, sometimes very severe in the acute stage and not infrequently fatal in children. Infection with the Shiga bacillus is nearly always a serious affair, occasionally seen in temperate climes but usually met with in the tropics. The stools may number 15 to 25 per diem even in the mild acute cases, and there is considerable rectal disturbance.

The presence of many pus cells as well as endothelial cells in a stained smear of dysentery stools is in itself a valuable differential diagnostic sign favoring the bacillary rather than the amebic type of infection. Stitt[5] describes this smear as

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75 per cent polymorphonuclears showing signs of degeneration but at times these cells similate a fresh pus smear.

The proctoscopic examination is a valuable aid in diagnosis of the acute case of dysentery. The mucous membrane is usually extensively but superficially ulcerated. These ulcers bleed and the surrounding mucous membrane is highly inflamed and presents a granular appearance. In the chronic case the mucous membrane may show no ulcers but there is a granulation tissue replacement and considerable hyperemia.

The diagnosis of bacillary dysentery is generally made on the blood serum agglutination test, it being difficult to isolate the causative organism except in the best equipped bacteriological laboratory, especially in the chronic cases. The agglutination reaction alone will carry with it more or less limited diagnostic significance dependent on the dilution of the agglutinating serum and the type of organism being tested. For example, with the Shiga bacillus it is considered diagnostic if the blood serum completely agglutinates in a low dilution of 1:50. With the Flexner bacillus, it is necessary to obtain agglutination in dilution up to 1:100.

Within the first few days of an acute bacillary dysentery, the agglutinins may not develop.

Cultures are of paramount importance in the diagnosis of bacterial dysentery. In the bacillary types, positive cultures are more frequently obtained from rectal contents and especially ulcer scrapings than from stool specimens. Delay in the examinations of stools accounts for many negative results. Fletcher and Jepps[6] demonstrated that the Shiga bacillus in acute dysentery will disappear from the stools within twenty-four hours in 10 out of 15 cases; in 4 they were present on the second day, and in one they survived until the third. The Flexner bacillus lived considerably longer, in the feces, than the Shiga type of organism. In more than half the specimens, 36 in number, the bacilli persisted for more than a week. In most of the specimens, the organisms were not found at every examination which was made during the time they remained alive in the feces; the reason for this was a sudden drop in the proportion of dysentery bacilli during the first thirty-six hours. This shows how important it is that bacteriological examinations be made with as little delay as possible.

Out of the 100 cases of bacterial dysentery seen by us, the predominating type is the bacillary. In the latter group the prevalent strain of infecting organism is the Flexner bacillus. About 75 cases of acute and chronic Flexner infections of the bowel were observed. The other bacilli of dysentery isolated from individual cases were the Shiga, the Duval and the Morgan. There undoubtedly are other cases of dysentery, not belonging to the bacillary or the amebic group, that are caused by bacteria and that are quite often unrecognized.

With reference to the unusual forms of bacterial dysentery, examples of which are herein described, it is our opinion that these are sometimes secondary to true dysentery.

DUVAL BACILLUS DYSENTERY

Since the discovery in 1904 of the lactose fermenting bacillus of dysentery by Duval and Schorer,[7] cases of dysentery due to this strain have been little seen in this country. Following the isolation of the organism from infants during an epidemic, Duval[8] isolated a similar strain from the contents and scrapings of the gut in a fatal case of dysentery in an adult. In 1905, Torrey[9] reported the finding of similar microorganisms in the stools of infants with diarrhea. Although several in question died, he would not admit an etiological relationship, because in the few instances in which the test could be done, the patient's serum either failed to agglutinate the bacillus or did so in low dilution only.

Simultaneous with our own investigations,[10] Nelson[11] studied cases of diarrhea in the Boston Children's and Infants'

Hospital during a period of six months. There were 32 cases reported as caused by *Eberthella paradysentery Sonne*. This late lactose fermenter is identical with the bacillus isolated by Duval and Schorer.[7]

While our group of cases in which this bacillus was isolated numbers only 5, they are reported for several reasons. First, there is an infrequency of the infection in this country, and these five represent the only ones studied in the South. There is no previous record of the disease occurring in several sporadic instances in the same locality. Of our 5 cases, 4 were in children under five years of age and only one in an adult. The bacillus of Duval was recovered from the rectal smear in each instance, and the patient's blood agglutinated the organism. The dilutions of the serum ran from 1:30 in one case and up to 1:200 in another. Of particular interest was the fact that the sera of these patients agglutinated the stock culture of the original strain isolated by Duval in 1904.

The symptoms in these cases were acute. The rectal mucous membrane showed numerous ulcers in each person. However, they ran a short course of a few days to one and one-half weeks' duration. The disease was mild and definitely self limited, which is unlike the dysentery produced by strains of Shiga and of Flexner bacilli that carry a high mortality in early childhood and with some tendency to become chronic in the adult.

CHRONIC STREPTOCOCCAL DYSENTERY

While different strains of streptococci are frequently found in the human intestinal tract, it is extremely rare to encounter a case of dysentery due to this organism. Bassler[12] names and discusses sixteen different varieties of intestinal streptococci that are more or less of pathogenic significance in connection with intestinal toxemia, the gut acting as a source of focal infection and especially as a source of toxin absorption. He believes the streptococcus represents the most important infecting organism in the intestinal canal and requires much attention in the examination of stools. However, this author does not cite any cases or does he refer to the possibility of the streptococci being the etiological factor in dysentery. In fact, we find that the literature for the past twenty-five years is practically devoid of any such references. For these reasons and because of the results of treatment, the following case of chronic streptococcal dysentery is reported:

Miss E. L. was first seen November, 1929, at the age of twelve. For the previous three months, she has been having frequent bowel movements (25 in twenty-four hours). The temperature rose to 102°–104°F. The stools contained mucus, some blood and purulent material. Frequent cross abdominal pains were present. A previous history was given of jaundice six years previous and pyelitis preceding.

The physical examination showed a well-developed but somewhat undernourished child. The head, including pupillary reflexes, throat, thyroid and lymph glands were normal. The tonsils had been removed.

The chest examination was negative, including skiagraph.

Abdomen: The liver was easily palpated on inspiration. There was no tenderness on pressure.

Reflexes were normal.

Laboratory Examinations: The urine showed a few pus cells. Gastric analysis (after test-breakfast) showed normal gastric digestion, pH 1.8. Repeated microscopic examinations of stools failed to show any amebae, or other protozoa. Stools contained mucus and some pus.

Blood pictures:

11/3/29	11/8/29	11/11/29
Reds		
5,975,000		
Whites		
16,250	10,250	7500
Hemoglobin		
85 per cent		
N. 48 per cent	N. 67 per cent	N. 57 per cent
S. M. 48 per cent	S. M. 31 per cent	S. M. 42 per cent
L. 4 per cent	L. M. 4 per cent	L. M. 1 per cent

Blood serum agglutination test for bacillary dysentery was positive in dilution 1:60 for Flexner bacillus. The Mantoux intracutaneous tuberculin test was negative.

The bacteriological examination of the stool revealed a very unusual finding of a pure culture of streptococci, there being no colonies of colon or other bacteria.

The patient's blood serum agglutinated this strain of streptococcus in dilution as high as 1:620. All other common strains of streptococci grown in the laboratory showed negative agglutination with the patient's serum.

The prostoscopic examination showed no ulcers or other rectal pathology. The barium enema examination showed normal haustrations of the colon.

From November, 1929, to May, 1930, very little improvement was noted. A high calorie non-irritating diet with colonic irrigations of acriflavine and other antiseptic solutions had been given during this period.

On May 5, 1930, an autogenous vaccine made with the strain of streptococcus isolated from the patient's stool was administered subcutaneously for the first time. From that date, when the stools numbered 8 to 12 in twenty-four hours and the patient weighed 60 pounds, until December 7, 1930 (a seven months' period), doses of the vaccine varying from 0.1 c.c. to 2 c.c., the large dose being followed by severe systemic reaction, were administered subcutaneously every three to four days. The improvement was marked with a decrease in the number of stools to 3 or 4 in twenty-four hours, with most of them formed, and a gain in weight of 20 pounds. A culture of the stool in September, 1930 (four months after vaccine therapy was started) showed a predominance of colonies of the same streptococci (serologically determined) and a return of the colon bacilli to the flora. Autogenous vaccine therapy has been continued and at the present writing the patient averages three firm stools a day with an occasional rise in temperature to 99.2°F.

CHRONIC SALMONELLA ENTERITIDIS INFECTION

Since the discovery of the *Bacillus enteritidis* by Gaertner in cases of meat poisoning, acute bowel infections due to this organism have been reported from nearly all parts of the world.

In a recent report from New Orleans, D'Aunoy[13] discussed the progress of several acute cases that were infected through the ingestion of cream-filled confections. It is noteworthy in his discussion that the immune bodies (agglutinins) disappeared from the blood within ten days after recovery. All of his cases recovered.

Under incidence, Bassler[12] states that *Salmonella enteritidis* is practically never found in chronic intestinal infection, usually only in meat poisoning from the use of infected meats from cattle.

The following case, encountered in our study of the bacterial dysenteries, represents the unusual occurrence of a chronic *Salmonella enteritidis* infection.

A dentist, seventy years of age, was first seen on August 8, 1930. For six months he had from 10 to 20 liquid stools per diem throughout the day and night. He felt a continuous pain in the right lower abdomen and a similar distress at times in the left.

Nothing of note was found on physical examination.

The gastric analysis showed a normal acidity.

Sigmoidscopic examinations revealed a diffusely injected rectal and sigmoid mucous membrane and a bloody mucous secretion in the lumen. Cultures of this material contained many colonies of *Bacillus enteritidis*. The patient's blood serum completely agglutinated this strain in dilution 1:60. The other members of the colon-typhoid group were not agglutinated. For nine months, the infection has persisted and the low grade chronic dysentery has been refractory to autogenous vaccine, foreign protein and other therapy. Withal the patient has gained 22 pounds on a high calorie non-residue diet.

STREPTOBACILLUS ASSOCIATED WITH CHRONIC DYSENTERY AND PYELOCYSTITIS

A married woman, aged thirty-seven, was seen on July 28, 1928. During a period of five years she suffered with abdominal distention and generalized abdominal pain, the bowels moving three to five times daily of a watery consistency. Raw fruits and sweets would cause a profuse diarrhea. Temperature

would rise in the evening to 99° and sometimes 100°F.

The physical examination of the head and chest was negative. The abdomen was generally sensitive to light pressure and quite painful in the left hypogastrium.

The pelvic examination was negative.

The rectal mucous was diffusely injected and inflamed.

The stool culture showed numerous colonies of a gram-negative, non-fermenting streptobacillus. The patient's blood serum completely agglutinated these organisms in dilution up to 1:80. There was a development of bladder symptoms, painful and frequent urination. Cultures of the catheterized specimens and right kidney urines were positive for the same non-fermenting streptobacillus isolated from the stools. The blood serum of the patient completely agglutinated the urinary organisms in 1:80 dilutions.

The bacillus of dysentery has been known to produce urinary tract complications. This is rare. In the instance of the colon bacillus infecting the kidneys and bladder, many authorities are of the opinion that the bacillus always migrates from the intestinal canal.

SUMMARY AND CONCLUSIONS

Several varieties of bacterial dysentery have been encountered in a survey of approximately 100 cases of this disease. The bacillary types, especially the strains of Flexner, Shiga and Duval, are endemic in the South and appear to be increasing in incidence. Recent reports from northern sections of the country would warrant careful investigation of suspicious cases for the possible determination of a wider dissemination of bacillary dysentery than is at present suspected.

Several unusual types of bacterial dysentery, in some instances with few previous clinical or bacteriological descriptions, are found to exist in the South.

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DISCUSSION

Dr. Asher Winkelstein (New York): In our climate, we find that chronic cases with bloody diarrheas, with or without fever, are usually instances of so-called non-specific ulcerative colitis. The old dispute has been going on for many years as to whether non-specific ulcerative colitis is or is not acute or chronic bacillary dysentery. In favor of the view that it is, is that the clinical, sigmoidoscopic, and, pathologic features certainly resemble very strongly, and in many cases possess the identical features of bacillary dysentery. However, the bacteriologic and serological evidence for this point of view has been lacking. Thorlaksen of Canada reported 4 cases that were considered typical non-specific ulcerative colitis in which he recovered the dysentery organisms.

The studies that are usually made are not sufficient to answer that question. To get a positive culture in bacillary dysentery it is necessary to take the culture from very fresh stools. If the stool is carried from the patient's bedside to the laboratory a half a block away one may miss a positive culture. It is very important to take repeated cultures of freshly passed stools. The agglutination reaction does not help as a rule. In our experience we have hardly ever, except in the special exceptions which I will mention, got a positive agglutination. Agglutinins often do not appear, particularly in the acute stages of disease and sometimes not even in the chronic.

At Mount Sinai Hospital in the last six months by careful bacteriologic investigation we have been able to prove, I think quite conclusively, that 4 cases of non-specific ulcerative colitis were definite bacillary dysentery, three Flexner, one Shiga. The patients all had the organism and all had positive agglutinations and the cross-absorption tests were confirmatory. We feel because of this and some other investigations which are in progress, particularly by means of bacteriophage studies, that non-specific ulcerative colitis is, in a certain number of the instances, what percentage we do not know as yet, bacillary dysentery either at the beginning or chronically so. And that, of course, is extremely important because of the isolation of a definite group and for the specific therapy.

Hurst, as you know, in England, and Crohn, in this country, have been ardent advocates of the polyvalent antidysentery serum. Occasional good results do not, of course, prove anything about the nature of the disease. We have treated several cases with the bacteriophage for the specific dysentery organism which was present or thought to be present. From a limited experience, we are not able to state definitely as to what the results are. All of us who see non-specific ulcerative colitis ought to study with the greatest care the bacteriology of the stools, particularly the very fresh specimens; and make repeated serologic tests with the point of view in mind that some of the cases of non-specific ulcerative colitis may be bacillary dysentery.

Dr. Moses Paulson (Baltimore): I am particularly interested in this streptococcal type of dysentery described by Dr. Silverman. The claim that streptococci are responsible for some type of dysentery is not new. With the intestine harboring myriads of organisms, it has not seemed possible to accept statements of the finding of a pure culture of one organism inhabiting an extensive area of involved bowel to the exclusion of all of the others. In five or six years' experience in the study of diarrheas in an experimental laboratory, I have never encountered a pure culture of any one organism. Frequently one sees in the literature the statement of the encountering of "almost a pure culture" in dysentery. "Almost a pure culture" of this or that organism, bacteriologically speaking, is not a pure culture. In many dysenteries the abundant growth of one organism at the expense of others in culture media favorable to the growth of that particular abundant bacterium, is not to be confounded with the actual bacteriologic state of affairs in the bowel proper; for example: certain cultural media may favor the growth of streptococci, yet streptococci may not be found to predominate in smears taken directly from the intestine. And again, in different cultural media, from material from the same source, another type of bacterium may preponderate.

However, in this instance, Dr. Silverman may have established his point. The bacteriological work appears to have been done very carefully, and the agglutination studies with the streptococci isolated are suggestive. I say suggestive because agglutination studies with streptococci are not satisfactory. These organisms, in the main, present poor antigenic properties, produce poor agglutination sera, and many of them even agglutinate spontaneously. The methods used to differentiate actual from spontaneous agglutination are not very satisfactory. I note that Dr. Silverman made efforts to overcome these difficulties in that he states that the streptococci alleged to be the etiologic agent in the type of dysentery he described, did not agglutinate in normal sera but did agglutinate in the patient's serum.

I cannot say that I am particularly impressed with the reported efficacy of vaccine therapy in the streptococcal type of dysentery. It is to be noted that the patient secured a remission upon the administration of vaccine after three or four months. Most of these cases secure more or less of a complete remission within this very period of time without vaccine. Remissions in many instances are spontaneous, I think, for they occur often regardless of the type of management and in spite of anything one might do.

Finally, it might be pointed out that the proctosigmoidoscopic pictures in organic diarrheas are not pathognomonic of any one intestinal involvement for we have seen cases both of amebic and bacillary dysentery which have presented appearances not unlike that of non-specific, or idiopathic ulcerative colitis.

Dr. T. R. Brown (Baltimore): Dr. Silverman brought up so many points of importance that I must say a few words about certain of those points.

In the first place, the practical point that the sigmoidoscope should be essential equipment in all diagnostic procedure to all clinicians; it adds so much to our knowledge.

In the second place, the extreme importance of making our studies, where possible, by means of fresh smears studied is the warm stage which increases tremendously the possibility or probability of finding the offending organism.

In the third place, the fact that the sigmoidoscopic picture as described by Dr. Silverman is very little different from that frequently described in certain cases of so-called non-specific ulcerative colitis, which calls attention to the fact it is not possible in every case to make a differential diagnosis between the two conditions.

In the fourth place, the very interesting case of streptococcal infection because it brings to the fore the moot question of whether streptococci can do this. I think Dr. Silverman has proved his case and yet in the great majority of cases we must take so-called streptococcal infection with many grains of salt.

The last point and the point I wish to ask Dr. Silverman's advice about is: in the treatment of these cases of bacillary dysentery, has he had results from serological treatment? Has he had results from vaccine therapy or has he followed the lead of certain of the workers in the Pasteur Institute and certain pediatrists in France, and found that this is one group of cases in which the bacteriophage has been effective.

Dr. Leon Bloch (Chicago): In all the patients in whom the diagnosis of ulcerative colitis is made, complete bacteriological and agglutination tests are carried out. In quite a few, the laboratory reported that streptococci were found and occasionally in pure cultures. We have made attempts to use a form of vaccine but met with failure in every case. In 5 of these patients positive agglutination tests with the Shiga bacillus were obtained. Four of these were acute cases. They started in the Fall after the patients had come back from a vacation in Southern Michigan. All had fifteen to twenty stools a day, typical mucopurulent stools of bacillary dysentery type. One of them had had a colostomy done a month before we saw him. He came into the hospital in a moribund condition and died from a perforation of the bowel before anything could be done. The 3 others in whom the diagnosis of bacillary dysentery had been made were treated with Flexner polyvalent antidysentery serum. Within the first twenty-four hours the number of stools dropped from fifteen and twenty to three or four and within forty-eight hours the stools had become partially formed. Two patients, sisters, one eighteen and one twenty, who had contracted the disease at the same time left the hospital after one week's stay with complete disappearance of all symptoms. In an other, a child who had been sick quite a while before she entered the hospital, the number of stools was reduced from twenty-five a day to ten a day after the first administration of the serum.

I call attention to these points because I believe that a good many of these patients who come to the hospital with a diagnosis of non-specific ulcerative colitis may have had a bacillary infection to begin with and subsequently a superinfection with whatever is the cause of the non-specific ulcerative colitis.

Dr. B. B. Crohn (New York): I should like to note that this festering sore of the causation of non-specific ulcerative colitis comes up again and again before the Association. If it is becoming apparent that dysentery organisms may be found in New York, are found in Chicago and are very definitely found in the South, it looks as if it would be likely that we will have to take out of the category of non-specific ulcerative colitis a certain percentage of cases, possibly only a small percentage, and group them possibly with the true dysentery cases.

I personally have been using polyvalent antidysentery serum since 1922, the idea originating first with Hearst in London. And I must say that I achieve in some of the cases very striking results, extremely striking. I never have been able to determine in my mind whether it is a non-specific result or a specific result though personally I have always felt the result was achieved through the non-specific protein of the serum rather than any specific effect of serum on possible existence of dysentery organisms in the body. However, I should like to encourage the use of polyvalent antidysentery serum and incidentally to ask Dr. Silverman, who has been handling these cases, just what his routine has been in the treatment of cases: whether he used the serum intravenously or intramuscularly; and to repeat the question of Dr. Brown as to the use of bacterio-

phage, because, if it is to be efficacious in any type of disease, it surely should be efficacious in this particular bacillary intestinal malady.

Dr. Daniel N. Silverman (*Closing*): With reference to the treatment of bacillary dysentery I said very little because of the discouraging results that are reported and which we have had. I think the only favorable results we have been able to obtain in acute cases of Flexner dysentery with polyvalent antidysentery serum, we have given from 30 to 60 c.c. daily intramusculary for the first four or five days.

With reference to vaccine therapy, Fletcher and Jepps in the Federated Malay States have had probably the largest series of bacillary dysentery in recent years and they are of the same opinion: that vaccine therapy is of no avail in the acute or the chronic cases of bacillary dysentery.

The bacteriological study is of great importance in the diagnosis of bacillary dysentery for the reason that we cannot depend absolutely upon the agglutinins, not only as to the type, but whether or not they are present, for this reason; that Lacy in the Philippines showed that there were some sixty different strains of Shiga organisms (I am sure there must be many of the Flexner bacillus) and the fact that we have been getting negative agglutinations in some of our cases, and that we suspected bacillary dysentery, led us on to more thorough cultural studies of bowel contents and we found Duval bacillus was present in some of our cases. So I think unless we have bacteriological studies, it is very difficult at best to make a positive diagnosis.

I have had no experience with the bacteriophage.

DISCUSSION OF DR JONES*

definite increase in urea, non-protein nitrogen and sugar without chloride or CO_2 change resembling the blood findings in experimentally produced peritonitis.

Upon a microscopic examination of the tissues of these animals, one is impressed with the tremendous changes noted in the liver and sometimes in the kidneys with definite areas in the pancreas which appear practically normal. The hepatic changes seem to run parallel with the blood chemical findings more than do the pancreatic changes. This suggests the cause of death as being due to an hepatorenal complex rather than to shock or peritonitis with tryptic digestion.

Dr. Clement R. Jones (*closing*): I have nothing further to say except to again call attention to the fact that the treatment in all of these cases is surgical and that I believe there are really two distinct varieties of this trouble: that which is caused by traumatism, whether the traumatism comes by pressure from within or whether it comes by injury from without or by the apoplexy of the gland as reported by Dr. Opie; and the infective inflammatory type caused by hematogenous or extending infection.

* Continued from p. 514.

STUDIES IN GASTRIC SECRETION

WITH A PRELIMINARY NOTE ON A NEW METHOD OF THERAPY FOR PEPTIC ULCER*

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NEW YORK CITY

APPARENTLY the three most important factors in the problem of the pathogenesis of peptic ulcer are (1) the mechanical factor, (2) the acid factor and (3) the tissue susceptibility.

As you know, in recent years, we have been particularly interested at Mount Sinai Hospital in the second, or acid, factor. Three years ago, before this Society, Dr. A. A. Berg presented the results of partial gastrectomy for ulcer, emphasizing the importance of subacidity or anacidity in the excellent results and particularly in the prevention of recurrence. At the same meeting I demonstrated, by means of pharmacologic studies, that the vagus nerve played an especially important rôle in the hypersecretion of ulcer patients. Dr. Eugene Klein then advocated the addition of left vagus nerve section to partial gastrectomy; with a resultant uniform achlorhydria in the group of humans in whom Dr. Berg carried out this procedure.

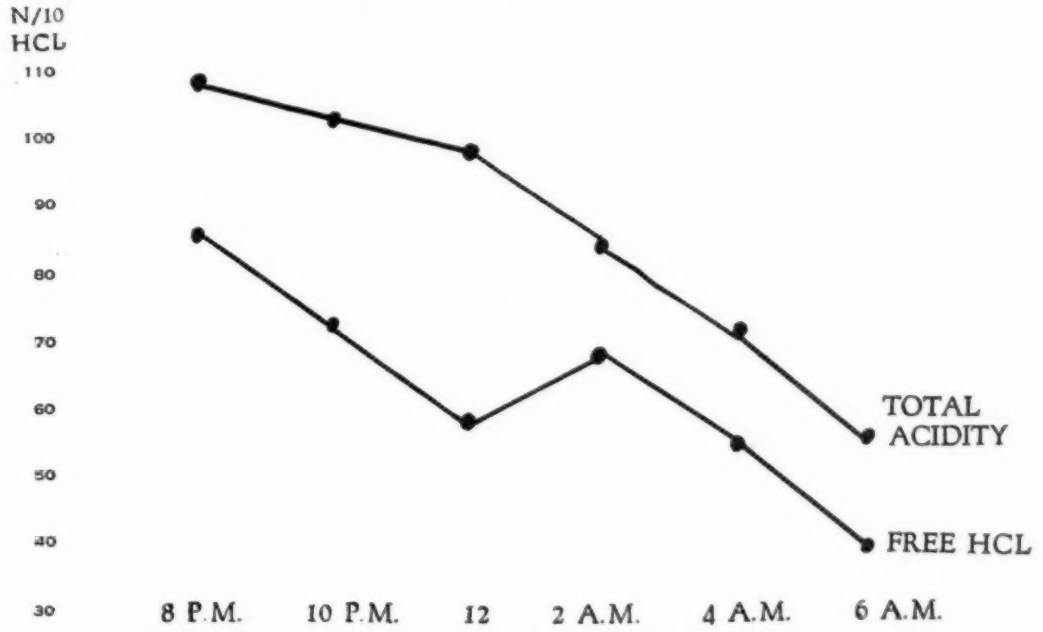

FIG. 1. Composite curve, "night Rehfuss," 12 duodenal ulcer patients.

Because of the importance of the vagus nerve in the mechanism of acid production, we have devised special test meal studies. Among them, it occurred to me to study the night secretion, i.e., the inter-digestive, fasting, or continuous phase of gastric secretion, presumably vagal in origin. At 4.30 P.M. the patient ate a light supper consisting of milk, eggs, toast and butter, and stewed fruit. The Rehfuss tube was passed into the stomach at 7 P.M. and a sample aspirated every two hours during the night. The patients usually slept fairly well. The illustrations show the results. In the first (Fig. 1), in duodenal ulcer, you see a high continuous curve; in the second (Fig. 2) in gastric ulcer, a moderate curve; in the third (Fig. 3) in the control

* Read before the American Gastro-Enterological Association, Atlantic City, N. J., May 4 and 5, 1931.

group, a very low one. In fact, four of the six controls did not show any free hydrochloric acid during the night and only 1

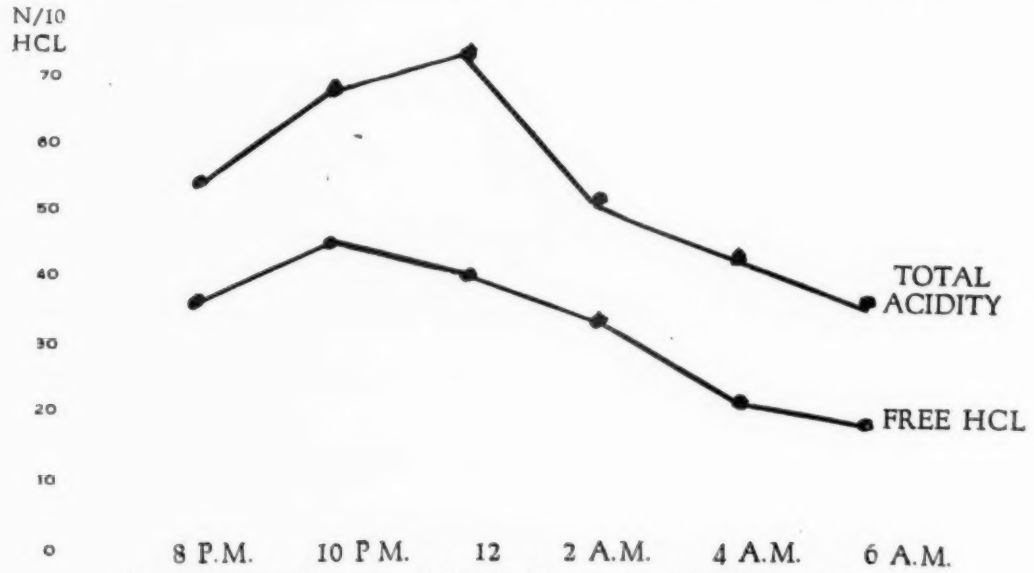

Fig. 2. Composite curve, "night Rehfuss," 5 gastric ulcer patients.

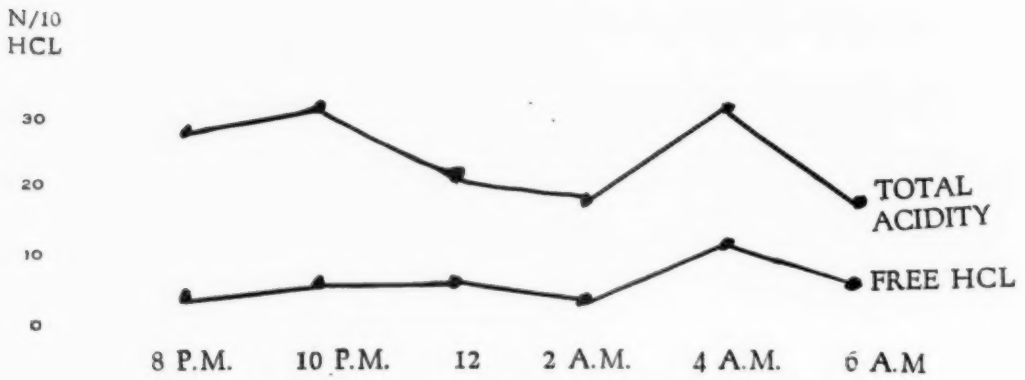

Fig. 3. Composite curve, "night Rehfuss," 6 control cases.

or 2 c.c. of gastric contents.

The theoretical significance of this cannot be discussed here because of the limitation of space. Practically, on the basis of this and other studies and also on theoretical grounds, I have suggested a new therapy of ulcer. This consists of a continuous, twenty-four-hour daily, Murphy drip, through a Rehfuss tube, of alkalinized milk into the stomach in duodenal ulcer, in gastric ulcer, and in jejunal ulcer. The details of the treatment must be omitted because of the lack of space. It may be said, however, that 12 patients with ulcer have been treated in the past few months and the method is definitely practicable and seems promising.

COMBINED ORAL & INTRAVENOUS CHOLECYSTOGRAPHY*

PERCY B. DAVIDSON, M.D., FERNANDO BIGURIA, M.D. AND JOSEPH ROSENTHAL, M.D.

BOSTON

CHOLECYSTOGRAPHY, since its introduction in 1924, has been practiced with varying degrees of success. Like many laboratory methods, it may be very helpful when interpreted in the light of clinical data, but quite misleading when its results are used as the only criteria. One of us has used cholecystography since its introduction and has found it decidedly helpful when the morphological and physiological data are considered in terms of the clinical history. A large part of the disrepute in which the method stands now has been brought upon it by observers who rely entirely on that notoriously capricious modification, the oral method.

The work to be reported in this paper concerns only ambulatory cases, and comes from two sources: a private office and an out-patient gastrointestinal clinic. Before the adoption of the combined method, it was the practice in the private office to use the intravenous method immediately in the study of all cases with definite gallbladder histories, as it seemed that suggestive pathology by the oral method meant very little; patients with other digestive symptoms were examined first by the oral method, and, in the event of an unsatisfactory test, were checked by the

FIG. 1. Shadow (before meal) of average density, as obtained by combined method.

FIG. 2. Same case as Figure 1, after fat meal.

* From the Gastro-Intestinal Clinic, Department of Medicine, Boston Dispensary. Read before the meeting of The American Gastro-enterological Association, Atlantic City, N. J., May 5, 1931.

FIG. 3. Cholecystogram (before fat meal) by combined method; two previous oral tests gave no filling.

FIG. 4. Same case as Figure 3, after fat meal.

FIG. 5. Negative shadow demonstrated by combined method, (before meal)

FIG. 6. Same case as Figure 5, after fat meal.

intravenous method. Infection, allergy, cardiac decompensation and coronary disease were usually looked upon as contraindications to the intravenous test. The hospital out-patients were all examined by the oral method; if the filling was not satisfactory, another test was done by the oral method, the supposition being that inability to fill on the two oral tests meant a pathological condition.

Since July, 1928, one of us, at the suggestion of Dr. L. R. Whitaker, has used a method which combines the usefulness of the oral method for ambulatory cases and the definiteness of the intravenous. In this method we give an intravenous dose sufficient to visualize the gallbladder, but small enough to eliminate reactions and hospitalization, and half the oral dose for fortification of the shadow. It was felt that if this method would eliminate hospitalization and present accuracy comparable to that obtained by the intravenous method, it would be particularly advantageous for ambulatory patients.

METHOD

On the day before the *x*-ray examination the patient eats a light low-fat supper at 4 P.M. and reports for the intravenous injection at 5 P.M. With the patient lying flat on his back, 1.5 gm. of sodium tetraiodophenolphthalein dissolved in 35 c.c. of distilled water, filtered and sterilized, are injected over a period of five minutes; the patient remains in this position for one-half hour before leaving the office. At 7 P.M. one-half the usual oral dose is taken in the usual way (keraphen, shadocol, and tetradol have been used); the patient is advised to rest during the evening and takes no food until after the *x*-ray examinations. The hospital patients received their oral doses before leaving, in order to eliminate misunderstanding.

At 9:30 A.M. the next day films are taken in the usual way, and, if satisfactory, the patient eats a fat meal. One hour after the fat meal, films are taken again; if the gallbladder has not contracted to at least half its size, further films are taken at intervals.

Fig. 7. Negative shadows demonstrated by combined method.

RESULTS

The results in 100 office cases with digestive symptoms not suggestive of definite gall-bladder disease, by our former procedure, of first the oral method, and, in the event of no shadow, a subsequent intravenous test, are recorded in Table I.

The results in 115 digestive (unselected) office cases studied by the combined method are shown in Table II.

Table III records the results in 50 consecutive hospital cases examined by the oral method and by another oral test (in a few instances by combined method).

The results in 50 consecutive hospital cases studied by the combined method appear in Table IV.

TABLE 1

ORAL METHOD IN OFFICE PRACTICE

Used routinely in cases without definite gall-bladder symptoms
(Definite cases were done by the intravenous method)
(Note: When no shadow was obtained, checked by intravenous test)

Case Number	Sex	Age	Weight	Clinical Picture			First Examination Filling		Repeat Examination Filling	
							By Oral Method		By Intravenous Method	
				Typical Gall Bladder	Vague Indigestion	Suggesting Other Digestive Syndromes		*Density (before Fat Meal)		Density (before Fat Meal)
1	F	28	152	..	+	.....	+	A		
2	M	29	140	..	+	.....	+	B		
3	M	46	140	..	..	Ulcer	+	B−		
4	M	27	144	..	+	.....	0	0	+	A
5	M	32	172	..	+	.....	+	B		
6	F	47	134	..	..	Colitis	+	D		
7	F	56	140	..	+	.....	+	D		
8	F	52	137	+	..	.....	0	0	Negative shadows +	D
9	F	36	138	..	+	.....	0	0	+	A
10	F	52	165	..	+	.....	+	B		
11	F	39	121	..	+	.....	+	A		
12	F	53	152	..	+	.....	+	C		
13	M	51	160	..	+	.....	0	0	Not checked	
14	M	36	184	..	..	Ulcer	0	0	+	C
15	M	45	145	..	..	Ulcer	+	C		
16	M	42	178	..	+	.....	+	C		
17	M	61	153	..	+	.....	0	0	+	B
18	M	45	150	..	+	.....	+	C		
19	M	46	127	..	+	.....	+	B		
20	F	41	128	..	+	.....	+	D		
21	M	32	137	..	+	.....	0	0	+	B
22	M	50	155	..	+	.....	+	C		
23	F	32	142	..	+	.....	+	B		
24	M	42	155	..	..	Ulcer	+	C		
25	F	27	145	..	..	Migraine	+	D		
26	F	44	148	..	+	.....	+	D		

TABLE 1 (*Continued*)

Case Number	Sex	Age	Weight	Clinical Picture			First Examination Filling		Repeat Examination Filling	
							By Oral Method		By Intravenous Method	
				Typical Gall Bladder	Vague Indigestion	Suggesting Other Digestive Syndromes		*Density (before Fat Meal)		Density (before Fat Meal)
27	F	63	127	..	..	Pernicious anemia	+	C		
28	F	36	131	..	+	.....	+	C		
29	M	30	191	..	..	Ulcer	+	D		
30	F	42	125	..	+	.....	+	D		
31	F	54	155	..	+	.....	+	C		
32	M	51	165	..	..	Abdominal pain of angina pectoris	0	0	+	B
33	M	35	135	..	+	.....	+	D		
34	M	41	145	..	+	.....	+	D		
35	F	18	89	..	..	Appendix	0	0	Not checked	
36	M	27	155	..	+	.....	+	C		
37	F	20	118	..	+	.....	+	D		
38	M	48	168	..	+	.....	0	0	0	0
39	M	36	147	..	+	.....	+	C		
40	M	49	143	..	..	.....	+	C		
41	F	20	146	..	+	.....	+	D		
42	F	45	132	..	+	.....	+	D		
43	F	50	169	..	+	.....	+	D		
44	M	30	105	..	+	.....	+	C		
45	M	29	167	..	..	Ulcer	+	C		
46	M	46	152	..	+	.....	+	C		
47	M	46	160	..	+	.....	+	A		
48	M	40	141	..	..	Digestive symptoms of cardiac failure	+	C		
49	M	32	124	..	..	Ulcer	+	G		
50	M	45	164	..	..	Ulcer	? Calculi	0	+	B

TABLE 1 (*Continued*)

Case Number	Sex	Age	Weight	Clinical Picture			First Examination Filling		Repeat Examination Filling	
							By Oral Method		By Intravenous Method	
				Typical Gall Bladder	Vague Indigestion	Suggesting Other Digestive Syndromes		*Density (before Fat Meal)		Density (before Fat Meal)
51	F	24	136	..	+	.....	+	B		
52	F	29	142	..	+	.....	+	B		
53	F	20	150	..	+	.....	+	D		
54	F	29	148	+	..	.....	?	O	+ (Stricture)	B
55	M	52	137	..	+	.....	+	C		
56	M	42	162	..	+	.....	+	D		
57	M	38	175	..	+	.....	+	C		
58	M	52	164	..	+	.....	+	D		
59	M	43	156	..	..	Ulcer	+ Negative shadows	D	+	B
60	M	31	174	..	+	.....	+	C		
61	F	22	127	..	..	Appendix	+	C		
62	M	42	167	..	..	Ulcer	O	O	+	B
63	M	27	142	..	+	.....	+	C		
64	M	37	157	..	+	.....	+	D		
65	M	47	161	..	..	Appendix	+	C		
66	M	33	156	..	+	.....	+	D		
67	M	31	190	..	..	Ulcer	+	B		
68	F	63	130	..	..	Ulcer	+	B		
69	F	53	148	..	+	.....	+	B		
70	F	75	152	..	+	.....	+	C		
71	M	46	185	..	+	.....	O	O	Not checked	
72	M	42	164	..	..	Ulcer	+	C		
73	F	28	123	..	+	.....	+	B		
74	M	47	154	..	+	.....	+	B		
75	F	42	143	..	..	Migraine	+	D		
76	F	32	130	..	..	Migraine	+	C		

Table 1 (*Continued*)

Case Number	Sex	Age	Weight	Clinical Picture			First Examination Filling		Repeat Examination Filling	
							By Oral Method		By Intravenous Method	
				Typical Gall Bladder	Vague Indigestion	Suggesting Other Digestive Syndromes		*Density (before Fat Meal)		Density (before Fat Meal)
77	M	44	162	..	..	Ulcer	Negative shadows 0	0	Not checked	
78	F	42	136	..	..	Ulcer	+	B		
79	F	42	137	..	+	.....	+	C		
80	F	34	135	..	+	.....	+	D		
81	M	56	167	..	+	.....	0	0	+	B
82	F	37	142	..	+	.....	0	0	+	B
83	M	40	147	..	..	Appendix	+	C		
84	F	20	127	..	..	Ulcer	+	C		
85	M	39	148	..	..	Ulcer	+	D		
86	M	53	147	..	+	.....	+	D		
87	M	40	148	..	..	Ulcer	+	D		
88	F	26	107	..	+	.....	+	C		
89	M	35	185	..	+	.....	+	D		
90	F	36	154	..	..	Ulcer	+	B		
91	F	29	142	..	+	.....	0	0	+	D
92	M	47	148	..	..	Ulcer	+	D		
93	F	51	170	..	+	.....	0	0	+	D
94	M	23	172	..	+	.....	+	C		
95	M	29	162	..	..	Colitis	+	C		
96	M	34	156	..	+	.....	0	0	+	C
97	M	37	180	..	+	.....	+	D		
98	F	32	142	..	+	.....	+	B		
99	M	42	185	..	..	Ulcer	+	D		
100	F	52	133	..	+	.....	0	0	+	B

* Density:

A, greater than spine.
B, equal to spine.
C, less than spine but clean-cut.
D, just visible.

TABLE II

COMBINED METHOD IN OFFICE PRACTICE

Case Number	Sex	Age	Weight	Final Clinical Diagnosis	Clinical Picture			Cholecystograms				
					Typical Gall-bladder	Vague Indigestion	Suggesting Other Digestive Syndromes	Filling	Density (before Fat Meal)	Intensity and Reduction in Size (after Fat Meal)	Calculi	
1	F	43	135	Duodenal ulcer	..	+	.....	+	A	A 1/3	0	
2	F	51	181	Duodenal ulcer	..	..	Ulcer	0	0	0	0	Note 1
3	M	40	174	Tuberculosis Hypertension	..	+	.....	+	B	B 1/2	0	
4	M	30	149	Migraine	..	+	.....	+	B−	C 2/3	0	
5	F	53	137	Mucous colitis (?) G.B. pathology	..	+	.....	+	A	A 1/2	0	
6	F	68	109	Auricular fibrillation Gastric ulcer	..	+	.....	+	A	A 1/3	0	
7	F	30	118	Appendix in R.U.Q. Chronic appendicitis	+	..	.....	+	B	C 1/3	0	
8	M	35	191	Psychoneurosis	..	+	.....	+	C	C 1/3	0	Note 2
9	F	43	157	Arthritis Spastic colon	..	+	.....	+	B	C 1/3	0	
10	M	26	182	Anxiety neurosis	..	+	.....	+	B	0	0	
11	M	33	163	Sino-auricular block	..	+	.....	+	B	B 1/3	0	
12	F	24	111	Pelvic pathology	..	..	Ulcer	+	A+	0	0	
13	M	26	159 3/4	Spastic colon Psychoneurosis	..	+	.....	+	C	D 1/4	0	Note 2
14	F	37	141	Arthritis Endocrinopathy	..	+	.....	+	B	C 2/3	0	
15	F	36	137	Cholelithiasis	..	+	.....	+	C	D	Negative shadows	Note 3
16	M	32	146	Gall-bladder pathology	+	..	.....	0	0	0	0	Note 3
17	F	43	89 1/4	Pulmonary tuberculosis	..	+	.....	+	B−	C 1/4	0	
18	M	26	151 1/4	Renal calculus	..	..	Appendix	+	C	C 1/3	0	
19	M	42	165	Duodenal ulcer	..	..	Ulcer	+	B	B 1/4	0	
20	M	28	158	Duodenal ulcer	..	..	Ulcer	+	B	0	0	

Table II (*Continued*)

Case Number	Sex	Age	Weight	Final Clinical Diagnosis	Clinical Picture			Cholecystograms				
					Typical Gall-bladder	Vague Indigestion	Suggesting Other Digestive Syndromes	Filling	Density (before Fat Meal)	Intensity and Reduction in Size (after Fat Meal)	Calculi	
21	F	45	181	Gall-bladder pathology	+	..	.....	0	No G.B. outline	No G.B. outline	Positive shadows	
22	F	29	117	Psychoneurosis	..	+	.....	+	A	B ¼	0	
23	F	37	154	Intestinal obstruction (partial)	..	+	.....	+	B	A ⅓	0	
24	F	43	121	Gall-bladder pathology	..	+	.....	0	0	0	0	Notes 3 & 7
25	F	45	144	Arthritis Spastic colon	..	..	.....	+	B	C ⅔	0	
26	M	62	141	Duodenal ulcer	..	+	.....	+	B	B ¼	0	
27	M	43	173	Psychoneurosis	..	+	.....	+	B	C ½	0	
28	F	44	165	Duodenal ulcer	..	+	.....	+	B	B ⅓	0	
29	F	30	102	Spastic colon	..	..	Ulcer	+	A+	A+⅕	0	
30	F	34	131	Duodenal ulcer	..	+	.....	+	B	C ½	0	
31	F	35	123	Duodenal ulcer	..	..	Ulcer	+	C	B ⅓	0	Note 5
32	F	26	124½	Duodenal ulcer	..	..	Ulcer	+	B	B ⅓	0	Note 6
33	M	37	170	Intestinal obstruction	..	+	.....	+	A	A ¼	0	
34	M	48	184	Duodenal ulcer	..	..	Ulcer	+	B	C ¼	0	
35	M	55	170	Duodenal ulcer	..	..	Ulcer	+	C	0	0	
36	F	53	150	Intestinal obstruction (partial)	..	+	.....	+	B	0	0	Note 4
37	F	40	140	Duodenal ulcer	..	..	Ulcer	+	A	A 1/6	0	
38	F	59	153	Renal calculus	..	+	.....	+	D	C ½	0	
39	F	29	155	Cholelithiasis	+	..	.....	+	B	B ¾	Negative shadows 0	
40	F	65	137	Psychosis cardiac	..	+	.....	+	C	C ½	0	

TABLE II (*Continued*)

Case Number	Sex	Age	Weight	Final Clinical Diagnosis	Clinical Picture			Cholecystograms				
					Typical Gall-bladder	Vague Indigestion	Suggesting Other Digestive Syndromes	Filling	Density (before Fat Meal)	Intensity and Reduction in Size (after Fat Meal)	Calculi	
41	F	59	137	Transcecal band	(?)	+	.....	+	B	B 1/3	0	
42	M	37	165	Tabes dorsalis	..	..	Ulcer	+	B	C 1/3	0	
43	F	44	145	Duodenal ulcer	..	+	Ulcer	+	C	C 1/6	0	
44	M	30	143	Duodenal ulcer	..	..	Ulcer	+	C	C 1/4	0	
45	F	32	124	Chronic appendicitis	..	..	Spastic Colon	+	B	B 1/4	0	
46	M	32	165	Anxiety neurosis	..	+	.....	+	B	C 1/2	0	
47	M	42	138	Spastic colon	..	+	.....	+	B	C 1/3	0	
48	M	27	172	Duodenal ulcer	..	+	.....	+	C	C 1/4	0	
49	M	45	160	Anxiety neurosis	..	+	.....	+	A	B 1/2	0	
50	F	34	124	Psychoneurosis	..	+	.....	+	C	C 1/3	0	
51	M	31	143	Psychoneurosis ? Chronic appendicitis	..	+	.....	+	C	C 1/6	0	
52	F	20	98	Pyloric ulcer	..	..	+	+	C	0	0	
53	F	38	114	Psychoneurosis Arthritis	..	..	Mucous Colitis	+	B	B 1/8	0	
54	M	28	153	Duodenal ulcer	..	..	Ulcer	+	C	D	0	
55	M	35	158	Labyrinthitis	..	+	.....	+	B+	B 1/3	0	
56	F	62	112	G. B. pathology Cardiac	+	..	.....	0	0	0	0	Note 7
57	M	53	178	Duodenal ulcer	..	..	Ulcer	+	A	B 1/4	0	
58	F	45	147	Spastic colon	..	+	.....	+	A	A 1/6	0	
59	M	27	159	Spastic colon ? Duodenal ulcer	..	+	.....	+	B	B 1/2	0	
60	F	26	155	Urinary pathology	..	+	.....	+	A	B 1/2	0	
61	F	65	120	Cholelithiasis	..	+	.....	+	B	B 2/3	Negative shadows	
62	F	48	118	Duodenal ulcer	..	..	Ulcer	+	C	C 1/6	0	

Table 11 (*Continued*)

Case Number	Sex	Age	Weight	Final Clinical Diagnosis	Clinical Picture			Cholecystograms				
					Typical Gall-bladder	Vague Indigestion	Suggesting Other Digestive Syndromes	Filling	Density (before Fat Meal)	Intensity and Reduction in Size (after Fat Meal)	Calculi	
63	M	40	157	Duodenal ulcer	..	..	Ulcer	+	C	C ¼	0	
64	F	40	110	Hypothyroidism	..	+	.....	+	D	D ¼	0	Note 5
65	F	58	141	Cardiac insufficiency	..	+	.....	+	C	C ¼	0	
66	M	58	127	Duodenal ulcer	..	+	.....	+	C	C ¼	0	
67	F	50	132	Chronic appendicits	..	+	.....	+	B	B ⅙	0	
68	M	53	124	Duodenal ulcer	..	..	Ulcer	+	B	0	0	
69	F	30	99	Psychoneurosis	..	+	.....	+	A	A ¼	0	Note 5
70	F	40	128	Spastic colon Psychoneurosis	..	+	.....	+	C	C ¼	0	
71	F	38	138	Cholelithiasis	+	..	.....	+	D	D ⅔	Negative shadows	Note 3
72	F	37	140	Cholelithiasis	+	..	.....	+	C	D ¼	Negative shadows	Note 3
73	M	38	163	Chronic appendicitis	..	+	.....	+	B	B ¼	0	
74	M	51	141	Hodgkin's disease	..	+	.....	+	C	C ½	0	
75	M	49	172	Duodenal ulcer	..	+	.....	+	B	B ⅛	0	
76	M	37	135	Psychoneurosis	..	+	.....	+	B	B ½	0	
77	M	55	220	Cardiac ? Coronary disease	..	+	.....	+	C	C ⅓	0	
78	M	29	160	Duodenal ulcer	..	..	Ulcer	+	C	C ¼	0	
79	M	36	190	Duodenal ulcer	..	+	.....	+	C	D ¼	0	
80	F	24	121	Neurosis	..	+	.....	+	C	C ¼	0	
81	F	40	140	Myxedema	..	+	.....	+	B	B ¼	0	
82	F	40	136	Cholelithiasis	..	+	.....	+	C	0	Negative shadows	Note 3
83	F	29	125	Duodenal ulcer	..	+	.....	+	B	B ⅙	0	
84	M	29	163	Duodenal ulcer	..	..	Ulcer	+	D	B ¼	0	Note 5

TABLE II (*Continued*)

Case Number	Sex	Age	Weight	Final Clinical Diagnosis	Clinical Picture			Cholecystograms				
					Typical Gall-bladder	Vague Indigestion	Suggesting Other Digestive Syndromes	Filling	Density (before Fat Meal)	Intensity and Reduction in Size (after Fat Meal)	Calculi	
85	M	32	135	Duodenitis	..	..	Ulcer	+	B	B 1/6	0	
86	M	39	168	Duodenal ulcer	..	..	Ulcer	+	B	B 1/6	0	
87	F	50	114	Chronic appendicitis	..	..	Ulcer	+	C	B 1/4	0	
88	M	39	153	Duodenal ulcer	..	..	Ulcer	+	C	0	0	
89	F	21	.....	Migraine	..	..	Migraine	+	B	A 1/3	0	
90	F	52	.....	Duodenal ulcer	..	+	.....	+	B−	0	0	
91	F	28	142	Psychoneurosis	..	+	.....	+	B	B 1/3	0	
92	F	38	120	Spastic colon ? Gall-bladder pathology	..	+	.....	+	D	D 2/3	0	
93	M	47	168	Duodenal ulcer	..	..	Ulcer	+	A	A 1/3	0	
94	M	48	200	Duodenal ulcer	..	+	.....	+	C	C 1/8	0	
95	F	54	124	Hypothyroidism	..	+	.....	+	D	C 1/3	0	
96	M	42	154	Spastic colon	..	+	.....	+	D	D 1/3	0	
97	M	44	163	Spastic colon	..	+	.....	+	B+	C 1/4	0	
98	F	52	124	Cholelithiasis Pyelitis	..	+	.....	+	C	C 1/3	Positive shadows	Note 3
99	F	46	108	Labyrinthitis	..	+	.....	+	B	C 1/6	0	
100	F	52	133	Tabes dorsalis	..	+	.....	+	B	B 1/3	0	
101	M	47	192	Subacute appendicitis	..	..	Appendix	+	C	B 1/4	0	
102	M	30	162	Duodenal ulcer	..	+	.....	+	C	0	0	
103	M	34	152	Psychoneurosis	..	+	.....	+	B	B 1/3	0	
104	M	47	155	Spastic colon	..	+	.....	+	C	C 1/3	0	
105	M	37	180	Duodenal ulcer	..	+	.....	+	C	C 1/2	0	
106	M	29	158	Psychoneurosis	..	+	.....	+	C	C 2/3	0	
107	F	49	136	Hypothyroidism	..	+	.....	+	B	B 1/2	0	Note 5

Table II (*Continued*)

Case Number	Sex	Age	Weight	Final Clinical Diagnosis	Clinical Picture			Cholecystograms				
					Typical Gall-bladder	Vague Indigestion	Suggesting Other Digestive Syndromes	Filling	Density (before Fat Meal)	Intensity and Reduction in Size (after Fat Meal)	Calculi	
108	F	41	126	Cholelithiasis	..	+	.....	+	B	B 1/3	One large negative shadow	
109	M	44	145	Duodenal ulcer	..	+	.....	+	B	B 1/2		
110	M	34	136	Psychoneurosis	..	+	.....	+	C	D 1/3		
111	M	42	180	Duodenal ulcer	..	+	.....	+	C	B 1/3		
112	F	58	152	Duodenal ulcer	..	..	Ulcer	+	B	B 1/3		
113	M	37	161	Psychoneurosis Hypothyroidism	..	+	.....	+	B	B 1/4		
114	M	37	148	Duodenal ulcer	..	+	.....	+	A	A 1/8	.....	Note 4
115	F	38	140	.....	..	+	.....	+	B	B 1/6		

1. Cholecystostomy nine years before, called normal gall-bladder.
2. No immediate reaction to intravenous dose; two hours after oral dose: nausea, vomiting and diarrhea.
3. Confirmed at operation.
4. Two previous oral examinations suggest pathology.
5. Phlebitis of injected vein.
6. Phlebitis and marked inflammation around injected vein.
7. Repeat by entirely intravenous test gave same results.

TABLE III

THE ORAL METHOD IN OUT-PATIENT HOSPITAL PRACTICE

Used routinely before the introduction of the combined method*

Case No.	Sex	Age	Weight	Clinical Picture			First Examination Filling	Repeat Examination Filling
				Typical Gall Bladder	Vague Indigestion	Suggesting other Digestive Syndromes		
1	F	24	211	+	..	.....	o	Not checked
2	F	48	181	.....	+	.....	+	
3	F	67	134	.....	..	Back pain	o	Not checked
4	M	53	170	.....	..	Ulcer	o	No filling on combined
5	F	40	145	.....	+	.....	+	
6	F	29	145	.....	+	.....	+	
7	M	34	160	.....	..	Duodenal ulcer	+	
8	F	50	189	.....	+	.....	o	Not checked
9	M	47	136	.....	..	Urinary pathology	?	+
10	F	56	141	.....	..	Chest pathology	o	Not checked
11	F	54	158	.....	+	.....	+	
12	F	60	159	.....	+	.....	+	
13	M	43	160	.....	+	.....	+	
14	F	67	188	.....	+	.....	o	o
15	F	24	128	.....	+	.....	+	
16	F	63	156	.....	+	.....	+	
17	F	30	110	R.U.Q. pain	..	.....	o	No filling on combined
18	M	39	134	.....	+	.....	+	
19	F	53	162	+	..	.....	o	o
20	F	46	173	.....	..	L.U.Q. pain	o	Not checked
21	F	33	123	.....	+	.....	+	
22	F	41	165	.....	+	.....	+	
23	M	65	156	R.U.Q. pain	..	.....	o	o No filling on combined
24	F	50	153	.....	+	.....	o	Not checked
25	F	29	109	.....	+	.....	o ? Calculi	+

(* Note: When no shadow was obtained, checked by another oral test.)

Table III (*Continued*)

Case No.	Sex	Age	Weight	Clinical Picture			First Examination Filling	Repeat Examination Filling
				Typical Gall Bladder	Vague Indigestion	Suggesting other Digestive Syndromes		
26	F	37	153	.....	+	.....	o Negative shadows (?)	Not checked
27	M	24	162	.....	+	.....	?	Not checked
28	M	65	129	.....	+	.....	o	Not checked
29	M	57	181	.....	+	.....	o	Negative shadows on combined
30	F	44	128	R.U.Q. pain	..	.....	+	
31	F	62	162	.....	+	.....	?	Not checked
32	F	52	138	.....	..	Carcinoma panc. & diabetes	?	Not checked
33	F	48	167	.....	+	.....	o	Not checked
34	F	43	125	R.U.Q. pain	..	.....	?	Not checked
35	M	53	183	.....	+	.....	+	
36	F	38	166	+	..	.....	?	+
37	F	45	105	+	..	.....	+ Calculi	Not checked
38	F	37	162	.....	..	R.U.Q. pain 1 attack radiating down to pubis	+	
39	M	40	188	+	..	.....	Calculi o	Not checked
40	F	37	190	.....	+	.....	+	
41	F	40	162	.....	+	.....	o	Not checked
42	F	36	145	.....	..	R.U.Q. pain	o	+
43	M	34	114	.....	..	R.U.Q. pain	+	
44	M	58	150	.....	+	.....	+	
45	M	55	158	.....	..	R.U.Q. pain	o	+
46	F	40	138	.....	+	.....	+	
47	M	37	172	.....	+	.....	o	+
48	M	19	138	.....	..	R.U.Q. pain	+	
49	F	22	127	.....	..	Jaundice & R.U.Q. pain	+	
50	F	40	110	.....	+	.....	+	

TABLE IV
COMBINED METHOD IN HOSPITAL OUT-PATIENT PRACTICE

Case No.	Sex	Age	Weight	Clinical Picture			Cholecystograms				Remarks
				Typical Gall Bladder	Vague Indigestion	Suggesting Other Digestive Syndromes	Filling	Density (before Fat Meal)	Density and Reduction in Size (after Fat Meal)	Calculi	
1	F	39	130	.....	+	.....	+	A−	A−½	0	
2	F	40	159	.....	+	.....	+	C+	C−⅔	+	
3	F	49	170	.....	+	.....	+	C+	C−⅔	+	
4	F	41	145	+	..	.....	+	D	D same	0	
5	F	40	157	.....	..	Attacks of epigastric pain	+	A+	A ½	0	
6	F	40	151	R.U.Q pain	..	.....	+	C	0	0	Previous oral method showed no gall-bladder shadow
7	M	28	132	.....	..	Ulcer Hepatitis	+	A−	B+	0	
8	F	54	153	.....	+	.....	+	A−	A−½	0	
9	F	43	178	.....	+	.....	+	A+	D ¼	0	
10	F	48	138	.....	+	.....	+	C−	C+¼	0	
11	F	40	182	+ Jaundice	..	.....	0				
12	M	36	190	?	..	.....	+	B	C−⅙	+	
13	F	49	137	.....	+	.....	+	B−	B+¼	0	
14	M	50	130	.....	+	.....	+	D−	D−½	0	
15	F	39	136	.....	+	.....	0				
16	M	39	175	.....	..	Upper abdominal pain	+	D	0	0	
17	F	60	168	+	..	.....	+	B	B ½	0	
18	F	52	177	+	..	.....	0				
19	F	66	177	.....	+	.....	+	C−	C same	0	
20	F	65	127	.....	..	Colitis	+	C−	B−⅓	0	
21	F	49	....	.....	+	.....	+	A	A+⅓	0	

Table IV (*Continued*)

Case No.	Sex	Age	Weight	Clinical Picture			Cholecystograms				Remarks
				Typical Gall Bladder	Vague Indigestion	Suggesting Other Digestive Syndromes	Filling	Density (before Fat Meal)	Density and Reduction in Size (after Fat Meal)	Calculi	
22	F	40	145	.....	+	.....	+	B−	C+1/6	0	
23	F	48	.....	.....	+	.....	+	A	A+1/6	0	
24	M	41	145	.....	+	.....	+	B	0	0	
25	F	25	125	+	..	.....	+	C	C 3/4	0	
26	F	40	160	.....	..	Colitis	+	B	B+2/3	+	
27	M	44	141½	.....	+	.....	+	B	B−1/4	0	
28	F	47	165	.....	+	.....	+	A	A−1/4	0	
29	F	47	156	+	..	.....	0	...	.....	+	
30	F	34	130	?	..	.....	+	A	A 1/2	0	
31	M	25	125	.....	+	.....	+	A−	A 1/5	0	
32	F	45	145	.....	+	.....	+	C	C+2/3	0	
33	F	50	189	.....	+	.....	0 0	...	.....	0 0	No filling on two attempts by combined method
34	F	40	164	.....	..	History of jaundice Clay-colored stools	+	A	A 1/4	0	
35	F	56	165	.....	+	.....	0 0	...	.....	0 0	No filling on two attempts by combined method
36	M	63	109	.....	..	Carcinoma of pancreas	0 0	...	.....	0 0	No filling on two attempts by combined method
37	F	54	.....	.....	+	.....	+	A−	A+1/4	0	
38	M	54	107	.....	+	.....	+	C−	C+2/3	0	
39	F	33	91½	.....	+	.....	+	C−	B 1/6	0	
40	F	41	174	+	..	.....	0	...	.....	0	

TABLE IV (*Continued*)

Case No.	Sex	Age	Weight	Clinical Picture			Cholecystograms				Remarks
				Typical Gall Bladder	Vague Indigestion	Suggesting Other Digestive Syndromes	Filling	Density (before Fat Meal)	Density and Reduction in Size (after Fat Meal)	Calculi	
41	F	66	142	.....	+	.....	+	A+	A+½	0	
42	M	41	163	.....	+	.....	+	B−	B−⅙	0	
43	F	36	156	+	..	.....	+	C	C ½	0	
44	F	38	148	.....	+	.....	+	A	A ¼	0	
45	F	40	118	.....	+	.....	+	A	A ⅔	0	
46	F	38	138	.....	+	.....	+	B	B ⅓	0	
47	F	55	145	.....	+	.....	+	C−	C+½	0	
48	F	42	128	.....	+	.....	+	A+	A+½	+	
49	F	40	134	.....	+	.....	+	A	C ⅔	0	
50	..	..	...	.....	..	.....	+	B+	A ½	0	

SUMMARY OF RESULTS

ORAL METHOD IN OFFICE PRACTICE

Summary of 100 cases examined by oral method and repeat by intravenous method where necessary.

(Symptoms not those of definite gall-bladder disease)

First Examination

Satisfactory filling..... 79
No filling..... 20
Questionable filling..... 1
Questionable calculi (without gall-bladder outline)..... 1

Second Examination

Of those with no filling on first examination

By intravenous

Satisfactory filling..... 16
No filling..... 1
Satisfactory filling suggesting pathology..... 3
Not checked..... 4

Of one with questionable filling

Satisfactory filling..... 1

Of one with questionable calculi

Satisfactory filling without evidences of calculi..... 1

Density

A	3	4 per cent of the 79 filled cases
B	16	20 per cent of the 79 filled cases
C	32	41 per cent of the 79 filled cases
D	28	35 per cent of the 79 filled cases
O	21	21 per cent of the 100 total cases

COMBINED METHOD IN OFFICE PRACTICE

Summary of 115 unselected digestive cases examined by combined method, and checked by intravenous where necessary.

Satisfactory Filling..... 110
No Filling..... 5
Corroborating clinical story of gall-bladder pathology..... 4
Proved by operation..... 2
Checked by intravenous (same results). 2
Previous cholecystostomy..... 1
Calculi..... 9
Proved at operation..... 5
No operation..... 4

Negative shadows
With gall-bladder outline..... 7
Without gall-bladder outline..... 0
Positive shadows
With gall-bladder outline..... 1
Without gall-bladder outline..... 1

Density (before meal)

A	15	14 per cent of the 110 filled cases
B	51	46 per cent of the 110 filled cases
C	37	34 per cent of the 110 filled cases
D	7	6 per cent of the 110 filled cases
O	5	4 per cent of the 115 total cases

ORAL METHOD IN OUT-PATIENT HOSPITAL PRACTICE

Summary of 50 consecutive cases examined by oral method and repeat by oral and combined methods where necessary.

First Examination
Satisfactory filling..... 23
No filling..... 21
Questionable filling..... 6
Questionable calculi (without filling).. 2

Second Examination
Of those with no filling on first examination
Satisfactory filling..... 4
No filling
(Oral)..... 2
(Combined)..... 2
Negative shadows..... 1
Not checked..... 11
Of those with questionable filling
Satisfactory filling..... 3
No filling..... 0
Not checked..... 4
Of those with questionable negative shadows but no gall-bladder outline
Satisfactory filling..... 1
Not checked..... 1

COMBINED METHOD IN HOSPITAL OUT-PATIENT PRACTICE

Summary of 50 consecutive cases examined by the combined method, and in certain cases repeated.

Satisfactory filling..... 42
No filling..... 8
Questionable filling..... 0
Calculi
With gall-bladder outline..... 5
Without gall-bladder outline..... 1
Questionable calculi
With gall-bladder outline..... 2
Of those not filling on first examination (8)
Negative shadows in region..... 2
Typical gall-bladder history..... 2
Obstruction due to carcinoma of pancreas 1
Vague indigestion..... 1
Repeated with combined method (same results)..... 2

Density

A	17	40 per cent of 42 filled cases
B	10	24 per cent of 42 filled cases
C	12	29 per cent of 42 filled cases
D	3	7 per cent of 42 filled cases
O	8	16 per cent of 50 total cases

DISCUSSION

At this point, we do not wish to enter into controversial matters in diagnosis of gall-bladder pathology. There can be no doubt that those of us whose practice is largely medical, miss, because of over-conservatism, a certain number of pathological gall bladders. For example, it has been our policy to consider a normally filling and emptying gall bladder without calculi as definitely not the seat of disease; yet, we have had several such patients operated upon, when the clinical history was sufficiently definite, and have obtained complete relief from symptoms. On the other hand, we feel that pathology can be diagnosed more definitely by a well-done cholecystogram than at the operating table; here function, as determined by *x*-ray, is often more valuable than direct inspection.

The oral method is overwhelmingly the most popular, although our results demonstrate its indefiniteness, particularly in hospital outpatient practice. *X*-rays of the gall bladder require, in addition to sufficient opaque substance in the organ, considerable technical skill and care. In a hospital outpatient department, the pressure of work does not allow the necessary individual development of films, often so valuable in procuring satisfactory gall-bladder visualization, particularly with the less dense oral shadows. The patient's personal factors in the hospital outpatient department, such as linguistic and educa-

tional difficulties, make the oral procedure difficult. But even in the better-controlled office practice, where instructions are accurately observed, films developed individually, many techniques of exposure tried, and such helps as enemata resorted to, the oral method is indefinite. The combined method has shown an accuracy comparable to the intravenous by operative findings, intravenous checks, and correlation with the clinical facts.

Indiscriminate intravenous medication of any type has, with reason, been looked upon with disfavor. Contraindications such as infection, marked allergy, cardiac failure and coronary thrombosis should be heeded even with the smaller doses of the combined method, but it has been our experience that the marked digestive upsets occurring frequently with the oral method may present more of a risk than the intravenous injection, carefully and slowly performed.

Levene and Whitaker[1] have used a combined method with two-thirds of the oral and two-thirds of the intravenous doses, and have reported that their patients have been "singularly free from any of the reactions which may follow a full intravenous or a full oral dose." In our experience using only one half of each dose there have been several instances of phlebitis of the injected vein, and in one case a severely sore arm for two weeks. Except for one case which is very doubtful, we have had no general reactions following the intravenous injection, but digestive disturbances have occurred about two hours after the oral dose, comparable, though less in intensity, to those often obtained with the oral method alone.

The certainty of results, elimination of the necessity of hospitalization, and infrequency of reactions make the combined method suitable for the study of ambulatory cases. We do not, however, feel that the intravenous method can be improved upon for hospital in-patients.

[1] Levene, G. and Whitaker, L. R. New methods for the clinical study of the gall bladder. *New England J. M.*, 202: 203-14, 1930.

CONCLUSIONS

1. Cholecystography by the combined oral and intravenous method presents an accuracy comparable to that of the intravenous method.
2. It produces a higher incidence of filling and denser shadows than the oral method.
3. Reactions are infrequent; those present are apparently due to the dose taken by mouth.
4. It is time saving, requiring but little more than the oral method, yet requiring no repeat examinations.
5. Cholecystography by the combined oral and intravenous method is the most satisfactory means of studying ambulatory cases.

The kindly cooperation of Dr. J. H. Pratt, Physician-in-chief, and Dr. H. F. Friedman, Roentgenologist to the Boston Dispensary, is acknowledged.

CLINICAL REPORT ON

A URINARY ANTISEPTIC*

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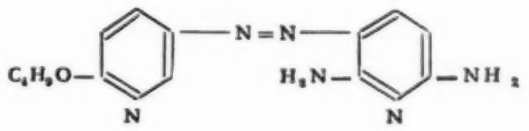
HOLLYWOOD, CALIF.

EACH of us is daily confronted with the problem of urinary antisepsis. This statement applies particularly to those of us doing urological work exclusively but includes also each and every one engaged in general practice. Cases of urinary infection, characterized chiefly by frequent and painful urination and by the presence of pus or bacteria, or both, in the freshly voided urine, are observed very frequently, in either sex, at any age. Those instances of urinary infection not frankly traumatic in origin, or due to faulty instrumentation, we are all accustomed to explain on a hematogenous basis by reason of an associated extra-urinary focal infection or an acute infectious disease. We have been able to establish a fairly definite relationship between urinary infections and certain predisposing or accessory causes, chief among which are imperfect urinary drainage, stone, tumor, foreign body and trauma. Our knowledge, however, as to the exact etiology and mechanism of urinary infections remains rather meager. And when we come to a consideration of the treatment of these infections, we encounter a problem even more baffling. Up to the present time there has been no known drug which might be given by mouth and which could be depended upon to prevent the growth and development of bacteria within the urinary tract.

In the early experimental work upon this subject by Davis, the ideal internal urinary antiseptic was defined as a chemically stable compound, comparatively non-toxic, and non-irritating to the lower urinary tract, which is eliminated, unchanged by the kidney, and which exerts a definite antiseptic action in high dilution in urine of any reaction.

Many drugs have been tried and found wanting, but during the past year we have had brought to our attention a substance appearing under the name of "niazo" which is briefly a diazotized pyridin product designed for oral administration as a urinary antiseptic. Chemical and pharmacologic nature show it to be a bright yellow micro-crystalline powder with the structural formula:



Niazo is well tolerated by more highly developed animals. Protracted administration in animal experiments showed that a dog will tolerate a dose of 120 mg. per kilo daily, over a period of thirty days without showing symptoms of kidney irritation. The administration of a single dose of 0.5 gm. per kilo was tolerated without any reaction. Only larger doses produced secondary effects such as diarrhea and vomiting.

Niazo is quickly absorbed, it is eliminated chiefly through the kidneys, partly through the liver. After the administration of the drug the urine shows a reddish-yellow color. It is necessary to keep this in mind, because it avoids mistaking it for biliary pigment or blood in the urine.

A sufficient adult dosage is 2–3 tablets after each meal but larger doses than this have been given in our series without toxic symptoms. It has also been found that the best results are obtained when the patient limits his fluid intake to about 1500 c.c. in the twenty-four hours. Most patients report after twenty-four hours a lessening in bladder spasm and note a soothing effect

* Submitted for publication November 13, 1931.

TABLE 1
CASES TREATED WITH NIAZO

Case	Sex	Age	Organism	Diagnosis	Treatment Before Drug was Given	Duration of Disease	Length of Medication	Number of Tablets Daily	Results
3205	M	38	B. coli, Cocci	Pyelonephritis	Dil. ureteral stricture	1 yr.	8 wks.	8	Good
2148	M	53	B. coli	Acute cystitis	Prostatectomy	3 yrs.	3 wks.	6	Good
3108	M	61	B. coli, Cocci	Cystitis, Bl. tumor	Fulguration of growth	14 mo.	4 wks.	6	Excellent
*3261	F	62	Mixed	Rt renal calculus	Nephrolithotomy	2 yrs.	3 wks.	3	Fair
2968	F	29	B. coli	Cystitis, Pyelitis	None	3 wks.	17 da.	5	Fair
3190	M	35	Gonococci	Acute p. urethritis	Hot Sitz baths	6 da.	10 da.	6	Good
3302	M	18	Gonococci	Acute p. urethritis	Hot Sitz baths	3 da.	15 da.	6	Good
3332	M	27	Gonococci	Acute p. urethritis	Hot Sitz baths	4 da.	18 da.	6	Good
3207	M	44	Gonococci	Acute p. urethritis	Hot Sitz baths	3 da.	14 da.	6	Fair
2080	M	29	Gonococci	Prostatic abscess	Incision—drainage	16 da.	21 da.	6	Good
3301	M	20	Gonococci	Acute urethritis	Urethral irrigations	1 da.	14 da.	6	Excellent
*3330	M	26	Gonococci	Acute p. urethritis	Urethral irrigations	14 da.	7 da.	3	Good
3348	M	58	B. coli, Cocci	Acute cystitis	Removal pros. obstruc.	6 yrs.	20 da.	6	Excellent
3230	M	64	B. coli, Cocci	Chronic cystitis	Removal bl. calculus	15 mo.	21 da.	6	Good
3372	M	28	Gonococci	Acute p. urethritis	Hot Sitz baths	10 da.	7 da.	8	Excellent
2031	M	56	B. coli	Cystitis	None	3 wks.	14 da.	6	Excellent
3378	M	19	Gonococci	Acute p. urethritis	Hot Sitz baths	2 da.	10 da.	6	Good
3362	F	61	Mixed	Cystitis, Bl. tumor	Bladder resection	1 yr.	19 da.	6	Good
3433	F	37	B. coli	Acute cystitis	None	2 wks.	14 da.	6	Excellent
3535	F	27	Cocci	Cystitis, Pyelitis	None	12 da.	17 da.	6	Excellent
2825	M	66	Mixed	Pyelonephritis	Ureterolithotomy	3 wks.	23 da.	6	Good
3503	M	64	B. coli	Chronic cystitis	Prostatectomy	8 yrs.	18 da.	6	Excellent
3530	M	29	Gonococci	Acute p. urethritis	Hot Sitz baths	4 da.	10 da.	6	Good
3556	M	27	Gonococci	Acute p. urethritis	Hot Sitz baths	6 da.	15 da.	6	Good
3541	F	57	B. coli, Cocci	Acute cystitis	None	3 wks.	10 da.	6	Excellent
3554	M	21	Gonococci	Acute p. urethritis	Hot Sitz baths	4 da.	14 da.	6	Good
2427	M	26	Gonococci	Acute p. urethritis	Hot Sitz baths	2 da.	20 da.	6	Good
3514	M	34	Gonococci	Acute p. urethritis	Hot Sitz baths	3 da.	15 da.	6	Excellent
3547	M	34	Gonococci	Acute p. urethritis	Hot Sitz baths	3 da.	20 da.	6	Good
3542	M	30	Gonococci	Acute p. urethritis	Hot Sitz baths	2 da.	16 da.	6	Good
2904	F	72	Mixed	Cystitis, Bl. tumor	Fulguration	5 mo.	14 da.	6	Excellent
3480	F	33	Gonococci	Acute urethritis	None	7 da.	20 da.	6	Good
3490	M	34	Mixed	Acute cystitis	Dil. urethral stricture	3 wks.	12 da.	6	Good
3528	M	33	B. coli, G. C.	Prostatic abscess	Incision—drainage	2 wks.	21 da.	6	Good
3550	M	64	B. coli	Cystitis	Prostatectomy	2 yrs.	14 da.	8	Good
3496	M	26	Gonococci	Acute p. urethritis	Hot Sitz baths	3 da.	16 da.	6	Good
2531	M	75	Mixed	Cord bladder	None	2 yrs.	5 wks.	6	Unimproved
2670	F	52	Gonococci	Acute urethritis	None	7 da.	21 da.	6	Excellent
3412	M	30	Gonococci	Acute p. urethritis	Hot Sitz baths	3 da.	14 da.	6	Good
2118	F	35	B. coli, Cocci	Acute cystitis	None	3 wks.	20 da.	6	Excellent
2050	M	45	B. coli, Cocci	Prostatitis	Hot Sitz baths	9 da.	16 da.	8	Good
3401	F	44	Mixed	Bl. diverticulum	Diverticulectomy	3 yrs.	30 da.	6	Good
3236	M	35	Gonococci	Urethritis	Irrigations	2 da.	15 da.	6	Excellent
3416	M	35	Gonococci	Acute p. urethritis	Hot Sitz baths	5 da.	14 da.	6	Good
2877	M	30	B. coli, Cocci	Prostatitis	Prostatic massage	2 mo.	18 da.	6	Good
2060	M	61	Mixed	Prostatic adenoma	None	3 yrs.	30 da.	6	Unimproved
3486	F	56	B. coli	Cystitis	Irrigations	2 wks.	18 da.	6	Excellent
3475	M	30	Gonococci	Acute p. urethritis	Hot Sitz baths	7 da.	20 da.	6	Good
3408	M	43	B. coli, Cocci	Prostatitis	Massage	1 mo.	14 da.	6	Good
3522	M	23	Gonococci	Acute p. urethritis	Hot Sitz baths	3 da.	.....	6	Unable to follow
3516	F	22	B. coli, Cocci	Cystitis, Pyelitis	None	4 wks.	28 da.	6	Excellent
3478	M	39	Mixed	Cystitis	None	2 wks.	21 da.	6	Excellent
3510	F	43	B. coli, Cocci	Acute cystitis	Dil. urethral stricture	1 yr.	15 da.	6	Excellent
3485	M	33	Gonococci	Acute p. urethritis	Hot Sitz baths	3 da.	12 da.	6	Good
3487	F	38	Gonococci	Acute urethritis	None	1 wk.	14 da.	6	Excellent
3477	F	23	B. coli, Cocci	Cystitis, Pyelitis	None	2 wks.	16 da.	6	Good
3410	M	63	Mixed	Cystitis, Bl. tumor	Fulguration	1 yr.	21 da.	6	Excellent
3259	M	42	B. coli, Cocci	Bl. calculus	Removal of calculus	8 mo.	14 da.	8	Good
3529	M	85	Mixed	Chronic cystitis	Prostatectomy	5 yrs.	30 da.	5	Good
3424	M	25	Gonococci	Urethritis	Irrigations	4 da.	16 da.	6	Excellent
3000	M	73	Mixed	Chronic cystitis	None	2 yrs.	25 da.	6	Unimproved
3508	F	40	B. coli, Cocci	Pyelonephritis	Catheter drainage	3 wks.	20 da.	6	Excellent
3519	M	32	Gonococci	Acute p. urethritis	Hot Sitz baths	5 da.	15 da.	6	Good
3443	M	25	B. coli, G. C.	Prostatic abscess	Incision—drainage	3 wks.	21 da.	6	Fair
3474	M	27	B. coli	Pyelitis	None	2 wks.	25 da.	6	Fair
3337	F	22	Cocci	Pyelonephritis	None	4 wks.	33 da.	6	Good
3513	F	63	B. coli	Renal calculus	Nephrolithotomy	1 yr.	25 da.	5	Good
3492	M	27	Gonococci	Acute p. urethritis	Hot Sitz baths	3 da.	16 da.	6	Good
3432	M	32	Gonococci	Acute p. urethritis	Hot Sitz baths	5 da.	20 da.	6	Good
3521	F	46	Mixed	Renal calculus	Nephrolithotomy	3 yr.	20 da.	6	Fair

* Cases which showed some gastric distress.

or decrease in urethral burning. Freeing urine of pus and bacteria varied greatly. We have found niazo of greatest advantage in the acute fulminating, posterior gonorrheal infections. Large doses over a period of several days with hot Sitz baths give the patients more benefit than anything we have tried so far.

In all cases studied except those with acute urethral symptoms, a complete physical and urological examination was made to rule out or correct all urinary tract abnormalities.

Table 1 shows what was accomplished in 70 cases in which niazo was administered orally. In this chart practically every type of urinary infection is represented that the practitioner meets with in daily practice.

Judging from the table there was improvement, considered satisfactory in about 87 per cent of patients receiving the drug. The prompt effect of niazo on bacteria, especially cocci, was surprising. It was in gonococcal infections that niazo seems to have a real selective action.

In conclusion, I would only reiterate the fact that it appears, from present indications, that the introduction of the chemotherapeutic dye preparations heralds a new epoch in urinary antisepsis. The work done so far on drugs of this type has been most auspicious. It behooves clinicians to familiarize themselves with these newer agents and to apply them rigorously in order that a logical therapy in combating urinary infections may be established.

In this field of endeavor, there is cause for optimism rather than pessimism, for the reason that the one greatest obstacle has been surpassed. It has been conclusively demonstrated that there are several chemical compounds, one of these being the newer agent, niazo, which may pass through the gastrointestinal tract, the blood stream and the kidneys of normal human individuals, rendering the urine an unfit culture medium for microorganism, and in no way injuring the body. It has further been shown that in selected cases these drugs exert a curative effect upon inflammatory conditions in the urinary tract.

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TIDAL IRRIGATION & SUCTION APPARATUS FOR EMPYEMA*

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WE were impressed two years ago by Hart's[1] publication describing an apparatus for the treatment of empyema by tidal irrigation and suction. It seemed that the principles which he suggested were correct. I have modified Hart's apparatus in several particulars which, I believe, make the apparatus simpler in design and easier to assemble and operate. The patient can be easily transported to the roentgenological laboratory without detaching the apparatus.

A graduated flask containing the irrigating fluid is connected by means of a Y tube with the drainage tube that goes to the chest. A Hoffman clamp is placed between the irrigating solution and the drip connection in order to control the flow. The constant addition of fresh solution to the system needs only to be 20 to 30 drops per minute. Physiologic saline solution seems to be the most satisfactory solution for irrigation.

The outlet tube is used for siphonage as in all cases of closed drainage, but the amount of suction is controlled by the interposition of two bottles in the siphonage system. The first of these bottles is kept on a level with the chest of the patient and acts as a reservoir for fluid which goes in and out of the chest during inspiration and expiration. The second bottle is a water trap to control the amount of suction applied. It can be raised or lowered in order to secure any desired siphonage or suction. A water manometer is connected to the tidal wash bottle so that the amount of suction can be determined. The water trap is then adjusted so that the suction applied is only slightly more than that which normally exists within the empyema cavity. Maximal interchange of fluid between the chest cavity and the tidal wash bottle will be obtained when the suction that is applied does not exceed the mean pressure that exists normally in the pleural cavity. The manometer fluctuates with the changes in pressure in the system and thereby aids materially in adjusting the water trap to secure the proper amount of suction.

A waste bottle collects the overflow from the water trap or second bottle. The entire apparatus has been mounted on upright rods with adjustable clamps so that it can be fastened to any hospital bed. The patient can be moved in bed without disturbing the action of the apparatus (see Fig. 2).

The advantages of maintaining a subatmospheric pressure in the pleural cavity during the period of time that surgical drainage of the purulent material is required needs no further comment. The principal objections to the closed system of drainage have been (1) an inability to keep the drainage tube from becoming blocked with exudate, fibrin or pus, (2) the possibility of the formation of secondary collections because of too rapid expansion of the lung, (in acute cases, if the drainage tube is carried from the chest of the patient to a bottle on the floor the amount of siphonage is excessive and the lung is too rapidly sucked down to the position of the tube in the chest leaving purulent material in some parts of the

[1] Hart, D., Method of treatment (of empyema) by tidal irrigation and suction with results in 30 cases. *Internat. S. Digest*, 7: 3–11, 1929.

Hart, D., Acute empyema. *Arch. Surg.*, 17: 102, 116, 1928.

*This apparatus was developed at the University of Pennsylvania, Surgical Service B.

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empyema cavity undrained), (3) leakage about the tube in the chest, especially when irrigated under positive pressure, (4) technical difficulties in care of the drainage apparatus and the nursing care of the patient.

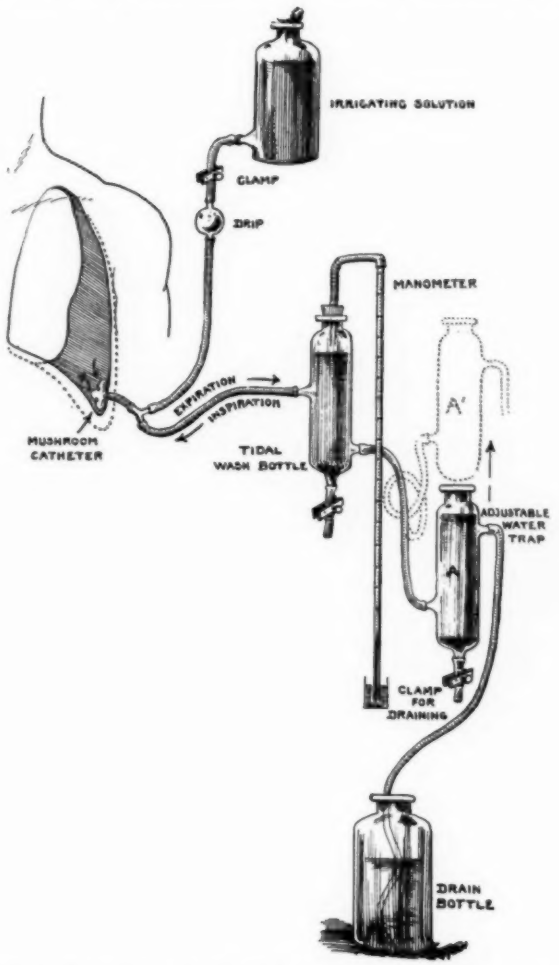

Fig. 1. Arrangement of bottles in empyema apparatus. Tidal wash bottle is level with chest of patient. Water trap is adjustable and controls amount of suction applied. Manometer is an open one so that it not only indicates variations in negative pressure created in system, but prevents excessive positive pressure in system when patient coughs as air will bubble out through manometer. All of the bottles are made of heavy pyrex glassware.

In the apparatus here described, use is made of the following factors: (1) a non-irritating fluid is slowly and continuously added to the system, (2) there is a continual washing or tidal flow of this fluid in and out of the chest with each respiratory act so that blockage of the tube is less apt to occur, (3) gradual, minimal suction re-expands the lung slowly and continuously, (4) the apparatus can be attached completely to the bed so that the care of the patient is not complicated. The only nursing requirement in connection with the apparatus consists in filling the irrigating flask with solution every six to eight hours. Dressings of the thoracotomy wound rarely have to be changed more than once or twice weekly. (5) Leakage about the tube in the chest is minimized since constant suction is applied and blockage of the tube rarely occurs. In adults a mushroom catheter is inserted through a large cannula and withdrawn so that the flange of the catheter fits snugly to the parietal pleural opening within the empyema cavity. This eliminates the possibility of too long a tube within the empyema cavity. The mushroom catheter can be inserted through a cannula without difficulty by passing a grooved director through

Fig. 2. Empyema apparatus showing connections to chest of patient and adjustable bed support.

its lumen until the rubber flange has been stretched out, thereby diminishing its diameter. In children a large Nélaton catheter inserted through a small opening in a piece of rubber tissue makes a satisfactory air-tight thoracotomy tube.

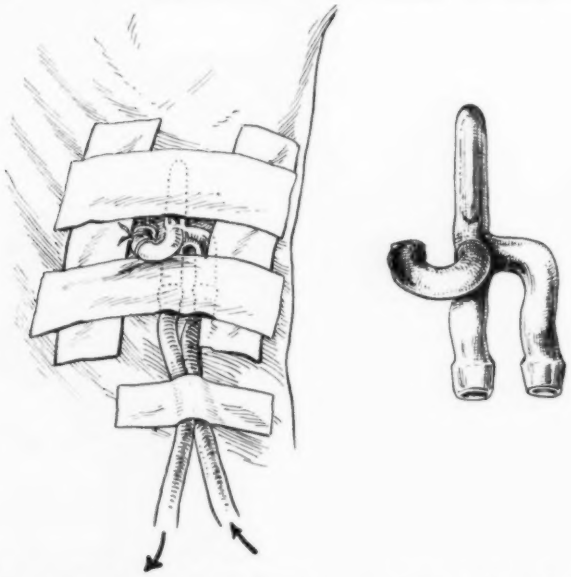

Fig. 3. Glass tube used to connect inlet and outlet tube with thoracotomy drain. Such a connection prevents kinking of thoracotomy tube and facilitates anchorage of tube to chest wall.

A curved glass connecting tube has been devised which prevents twisting or kinking of the drain at its point of exit from the chest (see Fig. 3). The drainage tube which enters the chest is cut short, 1.5 to 2 cm. from the chest wall and slipped over the curved end of the connecting tube. The rubber tube is secured in place by wrapping the tube at the point of overlap with silk thread. Separate openings provide for connection with the inlet and outlet tube. The addition of fresh solution to the system at a point near the empyema cavity is an important aid in the prevention of blockage of the thoracotomy tube. The entire connecting piece can be secured to the chest wall with adhesive tape. With such an arrangement it is possible for the patient to lie directly back on the drainage tubes or to move about in bed without the danger of kinking the tubes.

In the event of a bronchial fistula, the siphonage described here would, of course, fail to be maintained as air would gain entrance through the fistula. When a bronchial fistula exists, the water manometer is disconnected and additional suction applied through the rubber tube connected to the top of the tidal wash bottle. This additional suction can be supplied from a water suction pump connected to a nearby water faucet or by means of an electric suction apparatus. The adjustable water trap (A in Fig. 1) will continue to regulate the amount of suction. When the air that enters the system by way of the fistula does not exceed that leaving by the additional suction applied to the tidal wash bottle, air will be drawn up through the water trap and that amount of pressure controlled by the difference in the heights of the two bottles will be maintained. By sucking air out of the empyema cavity faster than it can enter by way of the fistula there will be a tendency for the cavity to decrease in size. When the fistulous opening on the lung surface reaches the parietal wall of the cavity, the fistula will close and additional suction will be unnecessary. Should continued suction fail to re-expand the lung, as may occur in chronic cases, one or another of the surgical procedures now used for obliteration of the cavity can be adopted.

AN UNUSUAL CASE OF

TUBERCULOSIS OF THE TROCHANTERIC REGION

BONE INFECTION NEAR THE JOINT*

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BONE infections near a joint offer several problems to the orthopedist. First, it is difficult to establish an early diagnosis. Later, when the *x*-ray shows the lesion, the etiology often remains obscure. The treatment, furthermore, demands judgment. It is hard to decide whether or not to operate. The optimum time for surgical interference varies with the individual case. All of these points are clearly illustrated by the case I wish to discuss. For nearly three years previous to the time that the patient was first seen, she had been treated by several physicians for tuberculosis of the hip. The roentgenogram, however, showed a lesion in the upper part of the femur, with the hip joint apparently free. At operation the lesion proved to be tuberculous. Later the hip became involved with a destructive arthritis typical of tuberculosis.

FIG. 1. *X*-ray of hip when first seen, one year after onset of symptoms.

FIG. 2. *X*-ray of hip three months after operation.

The patient, a girl five years of age, had fallen on a step and three days later had begun to limp. Soon after she began to complain of pain in the left hip; the pain would sometimes occur at night and awaken her. She was treated in turn by the local physician, an osteopath and a chiropractor, but continued to grow worse. After three months had elapsed the child was taken to a neighboring city to an orthopedist who applied a plaster-of-Paris cast to fix the hip. The parents were told that the child had a tuberculous hip. She wore a cast for four months and used crutches for three months longer. She had relief from her pain at once. When the cast was removed she walked without a limp and had no pain. She stayed well for nearly three months when the

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symptoms recurred, more severe than before. A year later the family physician noticed a swelling on the outer side of the thigh. He

Fig. 3. *X*-ray of hip nine months later.

incised this area and encountered pus. The wound drained for six weeks, during which time the patient was in bed with severe pain. A spica cast was again applied. The symptoms, however, persisted and the child gradually lost weight and strength. After three months she was brought for further consultation.

Examination showed a thin, pale child with a short loose-fitting cast on the left hip. The cast was removed and, in view of the history, the motion at the hip seemed unusually good. The roentgenogram showed an abscess in the upper end of the femur. In consideration of the history of the case it was thought best to treat conservatively for a while. There was a flexion and adduction deformity of the hip. Under general anesthesia the hip was easily brought to the mid-position; a plaster-of-Paris cast was applied from the axilla to the ankle, with immediate relief of pain. General hygienic measures, rest, fresh air, a high caloric diet, tonics, cod-liver oil and sunshine were prescribed.

The child gained in weight and seemed well in every way. The casts were changed and radiograms were made of the hip periodically. About six months after the application of the first cast the *x*-ray plate revealed a small dense area in the upper end of the femur. Three months later an area of absorption was visible around the area previously noted, and six weeks later the area of absorption was seen to be definitely increased. At the same time there was some swelling and tenderness present over the outer side of the left thigh below the greater trochanter. A provisional diagnosis of abscess in the upper end of the femur, probably tuberculous, was made and an exploratory operation advised.

A lateral incision exposed a cavity in the upper end of the femur which was filled with pus and contained two sequestra. The cavity when cleansed was found to be about the size of a hen's egg which, when we consider the age of the child, was relatively large. Anteriorly an opening the size of a dime connected with a well walled-off pocket of pus in the adductor group of muscles. The pus was removed and the cavity washed with iodine and alcohol; the wall of the bony cavity was made smooth with a curette and then wiped with iodine and alcohol. The cavity was made as shallow as possible by removing part of the wall; the remaining cavity was then lined with a thin layer of Bipp paste (iodoform, bismuth and paraffin). A fat graft was then swung down from above and another brought up from below to fill the cavity. The wound was closed and a plaster of Paris cast applied from the axilla to the toes.

A smear made of the pus taken from the femur showed staphylococci. The Ziehl-Nielson stain showed several rod-like, acid fast bacilli A blood agar plate was cultured and a guinea-pig injected. The culture showed grayish hemolytic colonies made up of gram positive cocci arranged in clusters. Two hours after the injection the guinea-pig died of peritonitis, and Staphylococcus aureus, identical with the original specimen, was demonstrated. Attached to the fragments of bone which had been removed was some grayish tissue resembling granular tissue; in this were found round or oval structures like tubercles, which contained

many epithelial cells and multinucleated giant cells; some granular tissue of the type which borders a tuberculous abscess, was also present. In specially stained section, inclosed within the giant cells, two rod-shaped, acid-fast bacilli were found. A guinea-pig inoculated with a salt suspension of pus from the femur was killed six weeks later. Many tuberculous changes were recognized in the lymph nodes, spleen and liver. Direct smears made of a lymph node showed many tubercle bacilli.

The rapidity with which the first guinea-pig died caused some concern as to the effect of so virulent an infection upon the patient. Confidence in the child's resistance was justified, however, and she remained comfortable. At no time did the temperature rise above 99.6°F. The morning temperature was normal, and after ten days the afternoon temperature also became normal. The leucocyte count dropped from 12,650 to 10,400; the hemoglobin was 67 per cent; the erythrocyte count was 3,440,000. Urinalysis showed no abnormal findings. The wound drained only a small amount of serum for a few days and healed without difficulty. On the tenth day the patient returned home. Six weeks later the cast was changed and a roentgenogram taken at the time showed a large cavity in the femur as well as a destructive arthritis of the hip, and the child was treated for tuberculosis of the hip. The hip remained free of pain and the child's general condition improved. She has been able to go to school and her development has been quite normal. The hip is in excellent position, no apparent shortening is present, and the roentgenogram shows the process arrested.

The patient thus presented an example of a bone infection near a joint, where the infection was tuberculous in origin and broke through to invade the hip joint to cause a destructive arthritis. Bone infections near the joint were discussed by Adrieu at the Eleventh French Orthopedic Congress in 1929. They were found to occur almost always below the eighteenth year, and most frequently in children from five to twelve years of age. Tuberculosis was the most common cause of the lesion. The hip, shoulder, knee, elbow, wrist and hand may be involved, and at times the lesions are multiple. In young children the epiphyseal disc acts as a protection against invasion into the joint. Adrieu also stated that the early symptoms were not characteristic, the pain varied a great deal, and disturbance in function was slight. The lesions in his experience never healed in less than one and a half years. His treatment consisted of absolute immobilization. If the lesion were definitely localized he urged an early operation to prevent invasion of the joint. He excluded involvement near the hip joint from this rule. In a discussion of the same subject, Froelich spoke in favor of conservative treatment. Sorrel operates only when the diagnosis is positively established. Nove-Josseraud tries conservative measures first and operates only when the joint is threatened by invasion. Rocher is in favor of an operation to save the joint but adds that the time for healing is not shortened by the operation. Martin du Pau advises the use of Masetig-plumbe (an iodoform-quajacol mixture), while Roederer lets the clinical findings of the individual case guide him as to whether or not an operation is indicated.

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The American Journal of Surgery is truly independent and enters into no "entangling alliances." It publishes many papers read before the leading surgical societies of the Country, but it is *not* "the official organ" of any organization. Every manuscript is selected by the editors, as worthy of publication—nothing is published merely because "it was read at the meeting."

EDITORIALS

IN the public press there appeared the statement of a physician of international fame to the effect that the current business depression has reacted favorably on the public health. The argument advanced was that since people could not indulge in luxuries that go hand in hand with boom times and since, due to lack of funds, many people were forced to go on simple, sparse diets, and instead of riding in automobiles, were walking to their places of appointment, the general health of the people was much improved. The conclusion drawn was that while these days might be troublesome ones to those engaged in the business of the nation, yet "the bright ray in the darkness" was that people were healthier than they had been in many years.

We doubt the accuracy of these theories and conclusions. It is a fact that the private and semi-private hospitals throughout the country have had a low census during the past year or eighteen months. On the other hand, the beds in charity hospitals have been filled and in many places there are waiting lists for those who wish to enter the institution for treatment. It is reasonable to assume that, good times or bad, people are suffering the ills common to mankind. Great strides have been made in preventive medicine and periodical health examinations have a strong foothold in the minds of the laity, but in times of depression one does not seek a physician unless he knows that he is ill. Only a man with a surplus in his pocketbook seriously turns to measures of prevention.

There is less surgery being done today than formerly, but no doubt there are thousands who will be operated on in the future because they did not have the mind and means to seek medical guidance at the present time.

It would be interesting to know whether, in two, three or five years from now, the percentage of cancer cases will show a vast increase, and we wonder if there are not many women who will be operated on for pelvic disorders that today could be so treated medically as to prevent future surgery. This holds true for the whole realm of surgical conditions. We feel that at the present time not only do conditions affect the pocketbooks of the people but they are neglecting their health, and the price they will pay in future complications will be heavy.

T. S. W.

AMERICAN PHYSICIANS

EPHRAIM McDOWELL

EPHRAIM McDowell, the father of gynecology, was born November 11, 1771 in Rockbridge Co., W. Va., of sturdy Presbyterian stock. He was the ninth of twelve children. After the Revolution, the family moved to Danville, Ky.

Ephraim's early education was meager. At the age of twenty he decided to be a physician. He returned to Virginia and entered the family of a Dr. Humphreys, of Staunton. After two years with this busy gentleman of mediocre talent he went to Edinburgh and began formal study. Here he remained two years. John Bell was his hero. Funds were not too plentiful, so Ephraim never took his degree, but returned home in 1795. He started practice in Danville, and was swamped with "a great burden of practice." For years he was the only surgeon in the state.

In 1809, when thirty-eight years old and after fourteen years in practice, he performed ovariotomy. A Mrs. Crawford consulted him for what was diagnosed as a large ovarian tumor. McDowell had already made up his mind, as a result of Bell's fundamental teaching, what he would do whenever confronted with such a problem. McDowell and his nephew, James, operated on her. There was no preoperative preparation beyond giving Mrs. Crawford a large dose of opium. "The patient being on the table, I marked with a pen the course of incision to be made; desiring him [nephew James] to make the external opening. I then took the knife, and completed the operation, as stated in the *Medical Repertory*. Although the termination of this case was most flattering, yet I was more ready to attribute it to accident than to any skill or judgment of my own; but it emboldened me to undertake similar cases; and not until I had operated three times . . . did I publish anything on the subject. I then thought it due my own reputation and to suffering humanity to throw all light which I possessed upon diseased ovaria."

McDowell sent a copy of his article to Bell in Edinburgh, and other copies to Wm. McDowell, his nephew and physician, and to Physick in Philadelphia. Physick never acknowledged its receipt. The nephew, however, took the story to Thomas C. James, and as a result, promptly published it in the *Eclectic Repertory*. The published cases were either unnoticed or not believed. The account sent to Bell fell into the hands of a Mr. Lizars, an Edinburgh surgeon, who was much impressed. The paper was published in the *Edinburgh Medical and Surgical Journal*. It was received with scorn. Before long, however, its value and worth were recognized. McDowell became a name throughout the medical world.

There is some discussion as to the total number of ovarotomies McDowell did. The number has been put at 13. We know 8 patients recovered.

In 1802 he married Sarah Shelby. They had eight children. In 1807 the Medical Society of Philadelphia sent him its diploma. In 1825 the University of Maryland made him an alumnus with the honorary M.D. After a short illness Ephraim McDowell died on June 20, 1830.

T. S. W.

[From Fernelius' Universa Medicina, Geneva, 1679.]

BOOKSHELF BROWSING

VIVISECTION AND OBSTETRICS*

J. P. GREENHILL, B.S., M.D., F.A.C.S.

CHICAGO

INTRODUCTION

ANIMAL experimentation has yielded an enormous amount of valuable information to obstetrics. To enumerate all these contributions is manifestly impossible, hence an effort has been made to select only the most important ones.

GLANDS OF INTERNAL SECRETION

By glands of internal secretion we mean glands whose specific products are transmitted directly to the blood or lymph instead of being carried to the exterior by a duct. In this group of glands are the following: ovaries, hypophysis or pituitary gland, thyroid, parathyroids, pancreas, adrenal glands, thymus, and placenta. Experiments on the glands of internal secretion have been performed in large numbers, especially during the last two decades. A fair proportion of this effort has been expended on pregnant animals.

OVARIES

The most important organs in women, from the point of view of the propagation of the human race, are the ovaries. Without ovaries, reproduction is impossible. Etienne Miroslaw, Grigorieff, Knauer, Francis H. A. Marshall and others have successfully transplanted the ovaries of animals from their original positions to other parts of the body. Joseph A. Long (1879) and H. M. Evans demonstrated that the ovaries of immature white rats can be transplanted into adult rats and there begin to function. Furthermore, W. E. Castle and others have transplanted ovaries from one animal to another of the same species, so that pregnancy followed the operations. In human beings transplantation of ovaries is still in the experimental stage, but the results so far obtained are encouraging.

Two ovaries are normally present, but a woman may be just as prolific if she has only one. Reproduction is the most important function of the ovaries. Furthermore, it is not the entire ovary which participates in the process of reproduction, but small yellow bodies, each of which is known as a *corpus luteum*. These bodies are due to the growth of so-called Graafian follicles, first described in 1672 by Reijnier De Graaf (1641–73), who demonstrated these vesicles in the ovaries and fallopian tubes of rabbits. One of these follicles originates as a group of cells and grows into a differentiated sac which con-

*This is the second of a series of articles on the value of animal experimentation in medical progress. The next article will appear in an early issue.

tains the egg, surrounded by fluid called the *liquor folliculi*. When the follicle bursts the egg or ovum is extruded and usually finds its way into one of two Fallopian tubes which lead directly to the cavity of the womb. In the Fallopian tube the ovum may be fertilized by a spermatozoon. In mammals, so far as is known, fertilization always takes place in the Fallopian tubes. According to George W. Corner the fertilized ovum proceeds exactly as the unfertilized one into the uterus on the fourth day, and this period of time is the same regardless of the widely variant length of the Fallopian tube in a number of different species of mammals. In mammals the ovum has an extremely short life, as shown by Hartman (1924) and Grosser (1924); hence the spermatozoon must fertilize the ovum within a few hours. After the expulsion of the ovum, the follicle in the ovary undergoes certain changes and becomes a corpus luteum. Normally there is only one fully developed corpus luteum present at any one time and it may be found in either the right or the left ovary.

A. Sokoloff (1861) was one of the first to experiment on the influence of extirpation of the ovaries during pregnancy. In 1896 he reported experiments on dogs which showed that removal of the ovaries early in pregnancy resulted in the absorption of the embryos; and he concluded that the ovary or the yellow body maintained the receptivity of the uterus for the development of an ovum. Fraenkel in 1903 advanced the hypothesis that the corpus luteum is responsible for the elaboration of a secretion which controls menstruation and the implantation of a fertilized ovum in the uterus. In 1910 he published his experimental work on rabbits in support of his theory. Leo Loeb whose experiments on this subject were performed on rabbits between 1907 and 1917 discovered the specific effect of the corpus luteum. He showed that the latter secreted a substance which sensitizes the lining of the womb so that it is changed into a layer, known as the *decidua*, which is capable of forming the placenta or afterbirth. He showed that if a foreign body is introduced into the uterus, the lining of the womb in contact with this foreign body assumes a decidual character provided there is a corpus luteum present. If there is no yellow body there is no reaction even after injection of ovarian extract. Albert P. Ancel (1873) and Paul Bouin (1870) performed similar experiments. Other experimenters who confirmed this work are Corner and Warren, R. Frank, and Long and Evans. Allen and Doisy injected the follicle fluid obtained from adult rats into immature albino rats and produced premature puberty. Allen, Pratt and Doisy and also Frank and his coworkers obtained a hormone from the follicle fluid, the corpus luteum and the placenta. Frank and Gustavson call this hormone the female sex hormone. Frank found that when this hormone is injected into immature female white rats it produces premature puberty and sexual maturity. Frank and Goldberger isolated this hormone from the circulating blood of women. They contend that the blood may be tested for the female sex hormone and thereby aid in the diagnosis of early pregnancy, the death of a fetus after the twelfth week, and the determination of sex in the presence of malformation or pseudohermaphroditism.

The general concensus of opinion is that menstruation is impossible without a corpus luteum but Corner has recently proven that in monkeys and also in the human being menstruation is possible without the yellow body. Pregnancy however is absolutely dependent upon the presence of mature follicles which contain the eggs and which are the fore-runners of corpora lutea.

In 1906 Marshall and Jolly confirmed Fraenkel's hypothesis by showing that spaying of dogs early in pregnancy caused death of the embryos and their resorption in the uterus. Hartman showed that in the opossum, removal of one ovary was

without effect on pregnancy but removal of both ovaries early in pregnancy invariably caused the death of the embryos. Nevertheless subsequent to the firm implantation of the ovum, the development of the fetus does not depend upon the corpus luteum, as shown by Kleinhaus and Schenk. Allen, Pratt and Doisy believe that the corpus luteum may be excised from a woman as early as twenty days after the last menstruation without interfering with normal gestation; but this is most exceptional. Walter Heape (1855) and Marshall studied in detail the anatomy of the oestrus cycle ("heat") in monkeys and many other animals and concluded that menstruation in women and in monkeys is analogous to the preoestrum in the lower animals.

In 1844 Bischoff demonstrated in rabbits the manner in which the ova escaped from the mature follicles and wandered into the Fallopian tubes. In 1880 Leopold showed that ova can travel a long distance and enter the tube on the side opposite the ovary from which they were expelled. This phenomenon has since been repeatedly shown to occur in the human. Corner and his associates have shown that there is a definite relationship between rhythmic contractions of the Fallopian tubes and the menstrual cycle, both of which depend upon the function of the ovaries. Wislocki and Guttmacher produced tubal contractions experimentally in pigs, and Keye and also Seckinger showed that these rhythmic contractions aid in the transportation of fertilized ova to the uterine cavity. Kok studied this phenomenon in cows, sheep, pigs and also human beings. He believes that the contractions of the tubes play an important part not only in the conveyance of fertilized eggs normally, but also in the condition known as tubal pregnancy in which the fertilized ovum remains in the tube, and sooner or later necessitates an abdominal operation in most instances.

Rubin insufflated the uteri of pigs with oxygen and observed rhythmic contractions of the tubes. Further experiments along these lines led him to his monumental contribution to medicine, namely a test whereby the patency of a woman's Fallopian tubes may safely and easily be determined without an operation. The Rubin test is not only a form of examination but also a therapeutic measure in the treatment of sterility, for a considerable number of women become pregnant soon after the test is performed.

HYPOPHYSIS OR PITUITARY GLAND

The hypophysis or pituitary gland is next to the ovaries the most important gland in the reproductive function. This gland is small, made up of two parts, one of which is continuous with the brain. Aschner extirpated this gland from pregnant dogs and found that all of them aborted. Harvey Cushing in 1912 also found this to be true but he demonstrated that no ill effects follow the extirpation of only part of this gland. Recently the deaths in the cases of complete extirpation have been attributed not to the removal of the hypophysis but to injury of a near-by important structure, the hypothalamus.

It was shown by Compte in 1898, that the hypophysis undergoes a marked hypertrophy during pregnancy, and the anterior lobe is exclusively responsible for this increase in weight. In women Cushing found that repeated pregnancies may cause such an enlargement of this gland that a transient, partial blindness may be produced by pressure of the gland on the large nerves which supply the eyes. Tandler and Gross pointed out that in some pregnant women there are abnormal manifestations of overactivity of the pituitary gland such as coarseness of the facial features, especially of the nose and lips and a thickening of the hands.

In 1909 a most important discovery was made concerning the hypophysis. H. H. Dale and also Fröhlich and V. Frankl-Hochwart found that administration of extracts of the hypophysis to experimental animals produced contractions of the

uterus during pregnancy and lactation. During the same year W. B. Bell injected pituitary extract into women and found that the result was the same as in the cat, dog, guinea pig and rabbit. Two years later J. Hofbauer reported very good results with these preparations and since that time preparations of the pituitary body have been used on an enormous scale in obstetrics. The outcome has been that not only has a great deal of benefit resulted from these preparations, but also much damage. The extracts when improperly used are productive of great harm but when properly applied are a great blessing. At present pituitary preparations are successfully used to initiate delivery, to accelerate labor under certain conditions, to control hemorrhage, to cause the uterus to contract at the time of a cesarean section, and to bring about the expulsion of the fetus and afterbirth which remain in the womb after a miscarriage.

We do not know the exact cause of the onset of labor but most likely the pituitary gland is at least partly responsible and this belief is the basis for the use of pituitary preparations for starting labor contractions. Dixon and Francis H. A. Marshall (1878) have shown experimentally that the ovarian secretion activates the pituitary gland, and that the latter in turn produces uterine contractions, thus having an important bearing on the onset of labor. Recently Jerlov (1926) performed a series of experiments on guinea-pigs and came to the conclusion that the stimulus for labor under normal conditions originates in the fetus.

Knaus in 1927 found that repeated injections of pituitary extract into pregnant rabbits early in pregnancy uniformly failed to disturb the gestation, but injections given late in pregnancy invariably resulted in delivery. These results may be paralleled in human beings, for it has been found that the nearer the time of the actual birth of the child, the more potent are the pituitary preparations. However, if abnormal contractions of the uterus are present in the early months as in cases of incomplete miscarriage, pituitary extract has a definite stimulating effect.

Aschheim and Zondek, who have done an enormous amount of valuable experimental work, were able to isolate hormones from the ovaries and from the hypophysis. They found that the pituitary hormones were greatly increased during pregnancy and were excreted in the urine. The animal experiments of the authors culminated in one of the most brilliant and practical advances made in this century, namely, a simple and reliable test for early pregnancy. Thanks to these investigations, pregnancy may now be detected as early as three days after the first menstrual period is missed.

THYROID GLAND

In 1896 Halstead showed that dogs in whom part of the thyroid gland had been removed were normal until they became pregnant. Then they showed symptoms of great deficiency in the secretion from the thyroid gland, and the symptoms disappeared after the birth of the puppies. These experiments proved that gestation leads to increased demands upon thyroid secretion. Halstead's work was confirmed by Marine and Lenhart in 1909. The latter investigators showed that when there was sufficient iodine in the diet, there was no increase in the size of the thyroids of their pregnant animals and the young were not born with goiters. Later when these same animals were placed upon a diet deficient in iodine the thyroid glands increased in size during pregnancy and some of the offspring had congenital goiters. The same phenomenon has been observed in human beings.

PARATHYROID GLANDS

Following the work of Frommer in 1906 and Adler and Thaler in 1908, it was shown that tetany (a disease characterized by painful, muscular spasms and paralysis, and often fatal) is due to absence or greatly defective secretion of small bodies

known as parathyroid glands. These glands are situated behind and are contiguous with the thyroid gland. They increase in size during pregnancy. Frommer, and Adler and Thaler found that in white rats portions of these glands may be removed without effect but when these animals become pregnant tetany develops. Luckhardt and Rosenbloom in 1922 showed that if the parathyroid glands are entirely removed from both pregnant and non-pregnant dogs, the dogs die within twenty-four to ninety-six hours. However, the dogs can be kept alive if given Ringer solution intravenously. The Ringer solution may be discontinued after forty to sixty days, and the animals will then remain alive and will not exhibit tetany. Lisser, Smith and Shepardson cured a patient who had tetany during pregnancy by means of parathyroid hormone. Dragsted and his co-workers have indicated the close connection between eclampsia (convulsions) in women and the toxemia which occurs during pregnancy in dogs in which the parathyroid glands have been removed.

PANCREAS

Diabetes is a fairly common disease. Because of the discovery of insulin a few years ago, much has been written about this illness even in lay magazines and newspapers and most laymen now know that the affliction is due to a disturbance in the internal secretion of the gland known as the pancreas. A large proportion of women who have diabetes are sterile and many more who become pregnant have miscarriages. Usually pregnancy in a diabetic woman aggravates the diabetes, hence pregnancy has frequently had to be interrupted. Since the advent of insulin, termination of gestation for diabetes has been infrequent. Experiments on dogs by Carlson and Drennan in 1911 yielded very interesting results. They found that in a normally developed fetus nearing the time of birth, the pancreas is so developed both qualitatively and quantitatively as regards the internal secretion necessary for normal sugar metabolism that the fetal pancreas acts as a residual pancreas of the mother when the entire pancreas has been removed from the latter. The internal secretion of the fetus passes through the uterine membranes in sufficient quantity to prevent diabetes in the mother.

ADRENAL GLANDS

There is experimental evidence to show that the adrenal or suprarenal glands also increase their activity during pregnancy. This augmentation is the cause of the increased pigmentation on the face, the nipples and the abdomen during pregnancy, and it also explains the exaggerated growth of hair frequently seen in pregnant women. Halban in 1903 demonstrated this increased growth of hair in animals.

Cybulsky demonstrated that the suprarenal gland through its secretion maintained the tonus of the muscular tissues of the body. Hence perhaps hyperactivity of this gland may be associated with the beginning of labor. O. Kamoto showed that adrenalin, the hormone of the suprarenal gland, excites the uterus of the cat, rabbit and guinea pig and inhibits the uterus of the rat. Recently Rucker showed that adrenalin also inhibits uterine contractions in women and it can therefore be used with great advantage in certain spastic conditions of the uterus.

PLACENTA OR AFTERBIRTH

The placenta or "afterbirth" is the organ by which a fetus is nourished while it is in the womb. The organ performs many functions such as digestion, respiration and excretion and hence is of vital importance. It is intimately connected with the specialized lining of the womb, the decidua, and if for some reason a large part of the placenta is destroyed or separated from its connection with the lining of the womb the child dies. Many animals devour the afterbirth immediately after they give birth. Hartman (1928),

who for the first time gives an exact account of gestation in monkeys, noted this phenomenon in his cases. In about a dozen monkeys he observed a marked reddening of the hips and buttocks ("the sex skin") during pregnancy, and this discoloration he attributes to the placental hormone. This same reddening was produced experimentally by Allen (1927) during the menstrual cycle and is due at this time to the hormone from the follicles in the ovaries.

BREASTS

The conditions which control the secretion of milk in the breasts have been the subject of much experimental work. The ovaries undoubtedly have an effect upon the breasts, since complete removal of the ovaries is followed by atrophy of the mammary glands. However, Mironow in 1894 proved that after apparently complete separation of the breasts from all their extrinsic nerves not only does the flow of milk,[8] if it was previously present, continue, but in operations of this kind upon pregnant animals the glands increase in size during pregnancy and become functional after childbirth.

TRANSMISSION OF SUBSTANCES FROM MOTHER TO OFFSPRING AND VICE VERSA

In 1892 Paul Ehrlich (1854–1914) demonstrated the passage of immune substances through the breast milk of the mouse. However, later observers showed that while this was true for ruminants it did not hold good for the human being. Ratner, Jackson and Gruehl, and Kuttner and Ratner have shown that in the guinea pig and the human being, substances pass from the mother to the offspring through the placenta but not through the milk. These authors corroborated earlier work of Rosenau and Anderson. Mother guinea pigs were sensitized with horse serum before pregnancy and all the offspring born of these mothers were sensitive at the time of birth. As soon as brought in contact with horse serum given in the vein, the offspring died in acute anaphylaxis or developed severe anaphylactic reactions. This transfer of protein hypersensitiveness was passive and lasted for only three months, exactly the length of time that passively transferred immunity would persist, and it could not be transferred to a second generation. These authors also showed that it was possible to sensitize a fetus while in the uterus of a mother who at the time of parturition was herself not sensitive. Since the permeability of the afterbirth in the guinea-pig and the human being are alike, the authors believe this active immunization in the womb explains the bizarre manifestations of infants when they come in contact with certain foods for the first time. These studies make physicians pay particular attention to any excess or cravings in a woman's diet during pregnancy and toward the influence that any injections given during pregnancy may have on the future sensitization of an unborn child.

A most fascinating series of experiments was performed by Sauerbruck and Heyde in 1910, after the publication of Basch on the famous Blatscheck sisters who were twins united at the hips. These investigators united rats to one another in such a way that they continued to live. If both animals were pregnant the occurrence of labor pains in one started a similar process in the other. If however, only one was pregnant, the initiation of labor pains in the gravid rat produced a serious illness in the other non-pregnant one. These observations according to the experimenters show that the cause of labor must be some substance which circulates in the blood and which is harmless to pregnant animals but poisonous to non-pregnant animals. However, Kross recently performed experiments on rats but could not verify these results.

STERILITY

Approximately 10 per cent of all marriages are sterile, hence sterility is a very

important problem. In recent years the question of diet as a cause of sterility has been extensively studied in animals. Herbert M. Evans and Burr have conclusively shown that certain vitamins are essential for fertility. They have shown that in rats vitamin E is an absolute necessity to prevent sterility. Well-known sources of this vitamin are wheat germ and butter. However, if substances containing this vitamin are mixed with large amounts of certain fats such as lard the effectiveness of the vitamin is destroyed. Reynolds and Macomber, who likewise studied the effect of the diet on the fertility of rats, conclude that the prolonged use of a defective diet may so effect the vitality of the germ cells that the product of conception will be able to attain only a certain stage of development before succumbing.

It is a common observation that very obese women are sterile but experiments on rats by Parkes and Drummond showed that an excessive degree of fatness does not necessarily lead to sterility and that fatness is more frequently a result than a cause of sterility.

Dittler (1920), McCartney (1923), Kovacs (1925), and others have been able to produce temporary sterility in rats by means of injecting the spermatozoa of the male into the female. As yet this method is not applicable for humans.

Not infrequently the desirability arises for inducing permanent sterilization of a woman. The fact that 42 operations have been devised for this procedure proves that not one of them is perfect. Most of the procedures aim at shutting off the lumen of the Fallopian tubes but the animal experiments of Fraenkel have shown that in a large proportion of cases the tubes regain their patency after operation.

MISCARRIAGE OR ABORTION

Closely allied to the question of sterility is that of miscarriage. As yet we do not know the cause of the majority of spontaneous early abortions. Hellendall in 1906 experimentally produced abortions in animals by means of bacterial injections. He showed that abortion followed infection of the contents of the pregnant uterus and that this infection may occur by three routes, first by way of the vagina, second by way of the mother's blood stream, and thirdly from the abdominal cavity by way of the Fallopian tubes as in cases of appendicitis. These three mechanisms are responsible for infection in the womb at any time of pregnancy or labor. Although all three means of contaminating the uterus occur in the human, the first one is the one most frequently encountered. This means that the physician must be extremely careful to avoid forcing bacteria into the vagina or uterus during his manipulations in this region.

Nickel and Mussey (1927) produced abortions in pregnant guinea pigs by injecting into these animals bacteria found in the tonsils and teeth of women who had had spontaneous miscarriages. This work confirmed that done by De Lee and Curtis on rabbits twenty years previously.

ACTION OF X-RAYS AND RADIUM ON THE FETUS

An enormous amount of experimental work has been done on this subject. In 1903 Bohn was one of the first to report abnormal development in the sea urchin after exposure of the eggs to the *x*-rays. Similar observations were made by Perthes on the ova of worms. The work of Richard Hertwig, O. Hertwig and G. Hertwig in this field are monumental. They proved that in amphibians retardation of embryonic development followed irradiation. Normal fertilized eggs subjected to radium produced deformed larvae and the extent of the deformity depended upon the amount of radium used and the duration of its action. Schaper confirmed this work and Tur reported deformities in the embryos of birds subjected to radium through the egg shell. Halsey Bagg found that pregnant rats when irradiated with

radium emanation near the end of pregnancy produced offspring that either died about ten days after treatment, or, if the young were alive after this period, they showed markedly deformed brains, blindness and sterility in both sexes.

The effects of exposure to the *x*-rays upon animal development are similar to those of radium. Perthes found monsters in the embryos of worms exposed to *x*-rays; Bordier noted abnormalities in silk worms, Gilman and Baetjer in amphibians and Baldwin in frogs. Hippel and Pagensteicher subjected pregnant dogs to *x*-rays and produced death and abortion of the embryos or cataracts in the eyes of the offspring. Regaud, Nogier and Lacassagne, Cohn Lengfellner, Krukenberg, Walter and also Little and Bagg likewise produced fetal abnormalities by submitting pregnant animals to the *x*-rays. All these experiments indicate that if irradiation occurs early in pregnancy, the fetus may be so injured that it dies and is aborted, or it may be born alive and show marked abnormalities. However, if the radiation is given late in pregnancy, the results may be of an insidious nature so that a normally-appearing offspring at birth may be stunted and show disturbances later in life. In recent years there have been clinical reports from physicians which show that where radium or *x*-ray was used early in pregnancy, great disturbances in the offspring were noted. In many cases, death and abortion of the fetuses have occurred. Irradiation late in pregnancy does not have the same tendency to produce gross developmental abnormalities in the child but at least some children subjected to radiation late in pregnancy have been born prematurely or have shown disturbances after birth. From the foregoing we may conclude that the therapeutic use of radium or *x*-rays in the region of the womb during pregnancy is fraught with great danger to the child in the womb. This danger, however, does not exist when one or a few *x*-ray pictures are taken during pregnancy because in these instances the exposure to the *x*-rays seldom last more than a few seconds at any one time.

A question of great interest is the following: Will a woman in whom a temporary cessation of the menstrual flow has been produced by the *x*-rays or radium give birth to abnormal babies after the return of menstruation? According to Wintz (1928) animal experiments have failed to prove definitely that abnormal fetuses are born after the return of the oestrus cycle which was suppressed by radiation. Likewise in women there is no unequivocal proof that *x*-rays or radium so injure unfertilized ova that damaged offspring will subsequently result when these ova are fertilized.

MONSTROSITIES AND TWINS

Much experimental work has been done on the production of monsters, notably by Child, and Stockard, both of whom seem to have discovered the same phenomena at about the same time. Stockard after many years of experimental work chiefly on fish came to the conclusion that changes in the conditions of moisture, temperature and oxygen supply in the environment of the developing embryos are the most frequent causes of embryonic death as well as of monstrous development. The primary cause of all abnormal developments is reduced by Stockard to a single factor, namely developmental inhibition or arrest. The type of deformity that results depends solely upon the exact moment when the interruption in development occurs. This author has produced different types of monsters at will by changing the time at which the retarding influences were brought into play. He has adduced experimental proof that there is a close relationship between identical twins and double monsters. Arey believes that Stockard's concepts apply equally to human abnormalities and twins. Newman who has done an enormous amount of experimental work on fish, worms, birds, etc., maintains for the armadillo at least, that

the essential feature of twinning is temporary cessation or radical retardation of development at a critical period. The nine-banded armadillo as first shown by Newman and Patterson in 1909 habitually gives birth to a litter of four offspring all of which are of the same sex and are strikingly alike. Other individuals who performed important work on monsters are Bellamy, Dareste, Gemmill and Kaestner.

Greenhill in 1923 attempted to correlate the association of monsters with a condition known as placenta previa in which the afterbirth is in the way of the exit of the child from the womb. This condition is usually a very serious one and causes the death of many women due to hemorrhage, infection and lacerations.

ANALGESIA AND ANESTHESIA DURING LABOR

As far back as history goes, notations have been made concerning the painfulness of childbirth, hence pain during the delivery of a child has been accepted as a normal phenomenon. In fact the contractions of the womb which produce the expulsion of the child are called "labor pains." Practically the only labors which are painless are those during which patients are given drugs or anesthetics.

In the first stage of labor, that is the period during which the womb prepares itself to expel the child, women are generally given drugs such as morphine, pantopon, scopolamin, atropin, heroin, magnesium sulphate, etc., which are given hypodermically and are known as analgesic drugs. These substances are helpful for they relieve most of the pain during labor. The most recent method advocated for rendering childbirth painless is known as the Gwathmey synergistic analgesia method and consists of hypodermic injections of morphine and magnesium sulphate and rectal instillations of ether, alcohol, quinine and oil. Animal experiments were performed to perfect this technique which is now extensively used.

In the second stage of labor, that is the period when the child is actually born, the pain is at its height and it is at this time that an anesthetic is given. The anesthetics generally used are chloroform, ether, nitrous oxide and oxygen, ethylene and oxygen and some form of local anesthesia. Sir James Y. Simpson in 1847 introduced the use of chloroform into obstetrics. Most women are now given an anesthetic during childbirth. At present chloroform is the one most infrequently used of all the inhalation anesthetics, because it has been found to be the most dangerous of all anesthetics. This was shown experimentally in pregnant dogs by Howland and Richards in 1909, Whipple and Sperry in 1909 and Whipple in 1912. More recently Stander, also experimenting with dogs, showed that damage to the organs was caused not only by chloroform but also by the other inhalation anesthetics as well. Furthermore, the injury found in the liver was similar to that produced by eclampsia, a disease of pregnancy and labor characterized by the layman as "convulsions" and one which exacts about 5000 lives every year in the United States alone. Boshamer also proved the harmfulness of ether on the human liver, hence nowadays we make every effort to employ some form of local anesthesia, especially in cases of eclampsia and the toxemias of pregnancy which may lead to eclampsia.

CHILDBED FEVER OR PUERPERAL SEPSIS

Childbed fever is a condition which causes the death of at least 6000 women every year in this country. Usually in this disease there are bacteria in the blood stream and efforts have been made to kill these bacteria with various drugs, chemicals and other means without, of course, harming the woman. Thus far the results have not been satisfactory. The most recent drug, mercurochrome, advocated by Young and White, and used extensively a few years ago, is not without danger when given intravenously. Since in most cases the organism known as the streptococcus is responsible for death in cases of

puerperal sepsis, many individuals have used some type of antistreptococcus serum. However, the results of serum therapy are not satisfactory. Tavel, Menzer and Aronson have each shown by means of animal experimentation that the serum used does not neutralize the bacterial toxins but merely produces conditions which increase the powers of resistance of the body.

DIET

It has always been of great interest to find out what effect the quantity or quality of the mother's food has on the offspring. Iron is of the utmost importance to the fetus and Fetzer in 1913 experimenting with rabbits showed that the amount of iron contained in the fetal tissue varies with the amount of iron in the mother's food. When the quantity of iron in the mother's diet falls below a certain minimum, the amount which is essential for the welfare of the fetus is taken from the maternal tissues. Zuntz in 1919 demonstrated in animals that during pregnancy a diet which was markedly deficient in one or more of the important constituents had no effect upon the weight of the offspring, but such animals were relatively sterile. Reynolds and Macombar in 1921 confirmed this work, but the original experiments were performed by Emmerich and Loew who in 1915 showed that calcium when fed to mice, guinea pigs and rabbits increased their fecundity.

There is a common belief among the laity that restricted dieting during pregnancy will bring about the birth of a small baby. Some physicians believe the same and many diets have been advocated for this purpose, notably that of Prochownick, a Russian. Slemons and Fagan and also Friedman have recently reported a reduction in the size of babies born of mothers who had been placed on a restricted diet. However, a marked reduction in the size of the baby cannot often be brought about by reducing the mother's diet. During the recent war, in spite of the prevalence of hunger and almost starvation in Germany, the babies born weighed just as much on the average as babies born before the war. We must nevertheless remember that overeating or excessive gain in weight during the second half of pregnancy is harmful, but chiefly because of its evil effect upon the mother and only indirectly on the child.

It is well known that early in pregnancy women often show lassitude, mental depression and loss of weight and that later during gestation the women feel very well both in mind and body. This phenomenon has also been observed in guinea pigs, dogs and rabbits by Hagemann Ver Ecke, Jägeroos, Murlin and especially by Bar. The excellent metabolic studies of Bar showed definitely that in pregnant dogs there is a storage of food in the second half of pregnancy which is more than sufficient for the needs of the fetuses, the afterbirths and their accessories. Hence, in the second half of pregnancy the mother gains and does not sacrifice herself for the sake of the species. Stander, Duncan and Sisson have shown that in dogs the heart performs much more work during pregnancy.

CONCLUSIONS

It is generally agreed that the knowledge of obstetrics today is very considerable but it is insignificant compared to what is still to be learned. As in the past, the solution of many unsolved problems in this field will come only from experiments upon animals. It may not be amiss to discuss briefly a few of the important problems.

The large question of involuntary sterility is just beginning to be studied. So much unhappiness is caused by infertility that it is imperative we obtain more knowledge with which to combat this condition. Many factors in sterility which are now being studied are the biochemistry, physiology and microscopic anatomy of the reproductive organs, the constitution of the individual, the compatability of the blood of husband and wife, artificial

insemination, the effect of diet and the use of the *x*-rays and radium. Hand in hand with the question of involuntary sterility is the matter of intentional infertility.

The matter of the determination of sex has a fascination for every one, lay persons as well as medical. Many individuals have devised methods of predicting the sex of a child before it is born but until the present time no method has been found reliable. Lüttge and von Mertz who have been using a chemical test of the mother's blood, claim to be able to predict the sex of an unborn child in almost every instance. Corroborative evidence of other investigators has failed to verify all the claims of the original experimenters but the test gives promise of being reliable when perfected.

The controlling factor in the determination of sex resides in the male element, as has been proved in an endless number of experiments on animals. In the latter, sex can be predetermined experimentally and animals may be changed from one sex to the other. Thus Witschi altered the temperature in which tadpoles were developing and the sex glands of the females gradually assumed a masculine character and the frogs emerged as males. Whether the sex can, and if possible should be, predetermined in humans is a question for the future to decide.

The cause of spontaneous abortions and miscarriages is unknown in most instances. The male partner is undoubtedly responsible for some miscarriages, but at present we have practically no way of proving this in the majority of cases for human beings. In domestic animals however, especially cattle, a great deal is known about the defectiveness of the male.

Not infrequently when babies are born dead near the end of pregnancy or die soon after birth, we can find no apparent cause for the death. New lines of investigation are necessary to solve these mysteries. Many babies that go beyond the normal time of confinement die before they are born but we do not as yet know why this occurs. Likewise we know comparatively little concerning the cause (except the small proportion due to syphilis), and almost nothing about the prevention of monstrosities. We have also much to learn concerning pregnancies which occur outside the womb.

Another and more important question which must be solved is why at a certain more or less specific time labor pains begin and a child is born. At present we have good reason to believe the stimulus for this activity comes from the hypophysis but we have not definitely isolated the substance which initiates the contractions of the womb. Because of this we have no safe and certain method of inducing labor when this becomes necessary.

Another large field for work is offered by the placenta and the bag of waters which surrounds the child in the womb. The amount of knowledge we possess today concerning the afterbirth, the membranes and fluid is infinitessimal compared with what we can still learn about these structures.

Douglas, a Scotchman said, "The pregnant woman ipso facto is apt to die," and many individuals believe this is true. Childbirth today, just as it always has been is associated with a certain amount of practically unavoidable damage to both mother and child. No other normal function of the human body is attended by so much injury. Why this should be we do not know, neither can we explain as yet why the blood of pregnant women shows certain reactions analogous to those shown only by the blood in infectious diseases and in cancer.

There could be mentioned many more problems which need elucidation but the foregoing brief review indicates that there are enough unsolved problems in obstetrics to keep those interested in research well occupied for many years. For the solution of most of these problems animal experimentation is absolutely essential.

BOOK REVIEWS

MEDICINE, SCIENCE AND ART, STUDIES IN INTERRELATIONS. By Alfred E. Cohn, M.D. Univ. Chicago Press, 1931, 212 pp.

This volume comprises the following six papers: "The Difference Between Art and Science in their Relation to Nature"; "The Development of the Harveian Circulation"; "Purposes in Medical Research"; "Medicine and Science"; "Physiology and Medicine"; "The Hierarchy of Medicine." They represent the authors' opinions along lines that have furnished food for thought for philosophers through the ages. Criticism or even discussion is rather disarmed by the author's frank statement that: "The chief reason for writing them [these essays] was to make clear to myself the views and opinions and the systematic relations of these bits of the world, at least, which required ordering within my own mind. Each having been for many years the subject of much inquiring. I welcomed occasions, as they arose, to reduce what I had to say to a form in which I could test the validity of my thought. If I share them now in this form, I do so for reasons which are common to all men but which I prefer not to disclose. Under the circumstances I need not protest that writing them has been a pleasure." And at the conclusion of his preface, after thanking his publishers, he makes a statement regarding them which we believe will also describe the feeling of the average reader of the book "their kindly and somewhat amused sympathy with the vagaries of an amateur author are quite beyond my praise."

Dr. Cohn has opinions of his own and is not afraid to express them. He has a wide acquaintance with the scientific literature of the ages but is in no sense a meek follower of authority or tradition. His writings are such as to stimulate his reader's imagination and encourage individual thinking, and we sincerely hope that he will have in his heart the same "kindly and somewhat amused sympathy with the vagaries of the amateur" reader (who may find difficulty in following all his rather profound and heavy lucubrations), that he bespeaks for himself as an author. The publishers are entitled to more than passing praise for a delightful piece of bookmaking.

HE MADE THEM TWAIN, A SOCIOLOGIST'S VIEWS ON MARRIAGE AND COMPANIONISM. By Bird S. Coler, LL.D. N. Y., Educational Press, 1931, 176 pp.

A distinctly modern book which is particularly refreshing in that it recognizes that all of our old institutions need not be thrown into the discard to insure the progress of civilization. Monogamous marriage according to Coler has stood the test of time and proved itself better than any substitute yet offered. Maintaining with incontrovertable logic that property rights are a basic necessity in the present-day scheme of things, he points to the necessity of the family unit as the keystone of such a structure and shows that the principles of monogamy are fundamental to the establishment of family responsibilities. Instead of making it easier to undermine and throw over these responsibilities the author advocates making marriage as it has come down through the ages a still more desirable and pleasant institution rather than to attempt to find a substitute for it as has been done by the radical school of modern sociologists, who, under euphonious terms, are in reality advocating and making attractive a return to early promiscuity and concubinage. Truly Mr. Coler's book is a wholesome and common-sense reminder that old fashioned decency have not yet been, and need not be, replaced by unbounded sexuality and licentiousness.

SIMPLE LESSONS IN HUMAN ANATOMY. By B. C. H. Harvey, M.D. Chicago, American Med. Assoc., 1931, 434 pp.

This is a narrative story of the anatomy of the human body so written as to be both interesting and instructive to the layman. Stripped of scientific verbiage the book is thoroughly accurate and scientific, and is just the book to place in the hands of those who wish to know something of the subject without desiring to master even the medical student's handbook. As Dr. Fishbein points out in the Preface: "Dr. Harvey has made the subject live," and many a layman will learn from this book that there is indeed more to the study of Anatomy than merely the dissection of the bodies of the dead, which is the usual concep-

tion of the subject. Here, at last, is a book that every physician may freely recommend to the patient who wants to know more about the structure and functions of his body.

Female Sex Hormonology. By William P. Graves, A.B., M.D. Phila., W. B. Saunders & Co., 1931.

For a better understanding of the factors playing the major parts in the fundamentals of those disorders peculiar to women we urge a consideration of William P. Graves' monograph.

Since the beginning of the century such giant strides have been made in relation to the factors of the internal secretions that it comes as a refreshing relief to pick up a work minus all padding and lopsided half-baked theory. It is a comprehensive review of the advances in the knowledge of female sex physiology and the rôle played by the ovaries.

The work is the result of a building-up of the notes used by the author in his classroom work. Feeling others might profit by reading them, as it is necessary to search through a scattered literature to get all known facts in one scientific corral, he has offered them in book form.

The chapters consider: Early History (Proof that the Ovary is a Gland of Internal Secretion); The Sexual Cycle in Animals: Sex Cycles in the Ovary (Ovulation, the Corpus Luteum); Sex Cycles of the Human Uterus and Its Correlation with That of the Ovary; The Search for the Hormones of the Ovary; The Discovery of the Hypophysis as an Agent in the Sexual and Reproductive Cycles (Pregnancy Test); The Hormones of the Anterior Lobe of the Hypophysis Identified; New Theories regarding Menstruation; New Theories regarding Parturition; New Theories regarding Lactation; Organotherapy (Amenorrhea, Dysfunctional Bleeding, Nervous Disturbances Related to the Menstrual Cycle). There is an interesting Glossary. The Bibliography offered is sufficient for the student if he desires to delve deeper into the subject. There is an index.

A well written, authoritative, up-to-the-minute, worthwhile work.

Gynecology and Urology for Nurses. By Samuel S. Rosenfeld, M.D. N. Y., William Wood & Co., 1931.

The author states in a preface that he has above all attempted to emphasize what the nurse most needs to know in order to be able to attend to her patients intelligently. In this the author succeeds admirably. He does not try to make a doctor out of the nurse, which, in these days, is a relief. Many intelligent physicians who have nursing and the teaching of nurses as one of their interests, complain that the undergraduate nurse is taught too much needless scientific hocus-pocus. Many who write books for nurses in their final effort give the impression they have thrown the book together in a haphazard manner. These faults are absent in Doctor Rosenfeld's small volume. And for this reason, not to mention that he has done his work with credit, we would recommend it to all pupil nurses.

BOOKS RECEIVED

All books received by The American Journal of Surgery are listed in this column as soon as possible after their receipt and this must be considered as adequate acknowledgment. Books that the Editor considers of special interest to our readers will be reviewed in a later issue.

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Applied Physiology. By Samson Wright. Ed. 4. N. Y., Oxford Univ. Press, 1931.

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I. Lesions Traumatiques. By G. Haret and Quenu J. Dariaux. Paris, Masson et Cie, 1931.
II. Lesions Non Traumatiques. By Etienne Sorrel and Dejerine Sorrel. Paris, Masson et Cie, 1931.

Avertinnarkose in der Chirurgie (Die). By W. Anschutz, K. Specht and Fr. Tiemann. Berlin, Julius Springer, 1930.

Cancer—What Everyone Should Know About It. By James A. Tobey. N. Y., Alfred A. Knopf, 1932.

Care & Feeding of Adults with Doubts about Children. By Logan Clendening. N. Y., Alfred A. Knopf, 1931.

Causation of Chronic Gastro-duodenal Ulcers. By J. Jacques Spira. N. Y., Oxford Univ. Press, 1931.

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Commoner Nervous Diseases. By Frederick J. Nattrass. N. Y., Oxford Univ. Press, 1931.

Congresos Argeninos de Cirurgia. Segundo Congreso Buenos Aires, 1930. By Eduardo Belaustegui. Buenos Aires, Las Ciencias, 1930.

Conquering Arthritis. By H. M. Margolis. N. Y., Macmillan Co., 1931.

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Description of the Planes of Fascia of the Human Body. By B. B. Gallaudet. N. Y., Columbia Univ. Press, 1931.

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Foundations of Medical History. By Sir D'Arcy Power. Balt., Williams & Wilkins Co., 1931.

Fundus of the Human Eye. By Ernest Clarke, N. Y., Oxford Univ. Press, 1931.

Guide to Localized Bi-terminal Tonsillar Coagulation. By L. Leo Doane. Butler, Pa., Washburn & Co., 1931.

Gynakologische Operationslehre. By Josef Halban. Berlin, Urban & Schwarzenberg, 1932.

Hay-fever, Hay-asthma. By William Lloyd. 3rd. Ed., London, Straker Bros. Ltd., 1931.

Health for Travelers. Edited by Alfred C. Reed. San Francisco, J. W. Stacey, Inc., 1931.

Hypertension and Nephritis. By Arthur M. Fishberg. 2nd Ed., 7th revision enlarged. Phila., Lea & Febiger, 1931.

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Intervertebral Discs. By Ormond A. Beadle. London, His Majesty's Stationery Office, 1932.

La Folie au XX^{e} Siecle. By A. Rodiet and G. Heuyer. Paris, Masson et Cie, 1931.

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PERIPHERAL NERVE INJURIES

LEWIS J. POLLOCK, M.D.

AND

LOYAL DAVIS, M.D.

THIRD INSTALLMENT

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Chapter VIII

EXAMINATION (*Continued*)

VIII. Vasomotor, Trophic and Secretory Disturbances

Numerous disturbances and changes of the nails, hair, joints and secretions in the vasomotor reactions and nutrition of the skin have been described as the result of peripheral nerve lesions. Considerable doubt exists as to the true nature of some of these disturbances. Some, perhaps, result directly from a lack of nerve supply but many are caused by other factors, such as injury to vessels or continued immobilization. The pathogenesis of these disorders is too controversial to permit of a definite opinion, and it is necessary only to point out their occurrence and in some instances to stress the conditions associated with their several appearances.

True vasomotor reaction disturbances may be demonstrated in the area of skin supplied by an injured nerve by recording the reactions to irritating substances, such as mustard oil, on the normal as compared to the injured side. On the normal skin, hyperemia with swelling and burning occurs; on the injured side there is no effect. Similar information may be obtained by the study of reactive hyperemia following freezing and stroking.

Disturbances in circulation are characterized chiefly by cyanosis, swelling, edema, hyperemia, local asphyxial attacks and gangrene. The cyanosis is accompanied by hypothermia and subjective coldness. It is increased by a dependent position of the extremity. The disturbance is not limited to the sensory distribution of the injured nerve but involves the whole affected extremity. The color varies from a reddish-purple tint to bluish-black. Often the area is succulent and when pricked with a pin blood gushes out. Such severe circulatory disturbances are rightly attributed by Bénisty and H. Meige to concomitant vascular lesions. Injury to certain nerves, for example the median, produces circulatory disturbances more than others.

Simons found that when the median and ulnar nerves were cut and the radial was intact vasomotor reactions were absent on the affected side, whereas with the radial alone involved no

FIG. 55. Trophic and vasomotor changes in skin after peripheral nerve injuries.

change occurred in the vascular reactions. Vasoconstrictor spasms are rare. (Fig. 55.)

In addition to the glossy skin already described under the chapter on Causalgia, Weir Mitchell noted the occurrence of

thickening and drying of the skin and failure of desquamation. Head has pointed out that failure of desquamation is commonly noted over the sensory supply of an injured nerve, even when a

FIG. 56. Vesicular eruptions and keratoses which follow peripheral nerve lesions.

superficial sensory nerve alone is severed. The skin becomes inelastic and the cracks are better marked, giving the surface the appearance of the skin of a toad. This dry, rough and scaly skin is a frequent accompaniment of peripheral nerve lesions, whereas the glossy skin is relatively rare.

Athanasio Bénisty is of the opinion that Weir Mitchell included in his cases of causalgia cases of glossy skin with pain due to vascular lesions. She states that glossy skin is relatively rare in pure painful lesions of the median and tibial nerves. We have described the appearance of glossy skin in the chapter

on Causalgia and referred to the fact that in our material glossy skin without pain occurred chiefly in lesions of the median and tibial nerves, just as did causalgia. We did not

FIG. 57. Hypertrichosis following peripheral nerve injury.

observe many cases of vascular lesions in this group. Of 30 cases of injury to arteries which necessitated ligation and were complicated by nerve injury, no cases of glossy skin appeared. We are inclined to believe that glossy skin and causalgia, alone or combined, are due to the same factor and result from injuries of the median and tibial nerves.

As an accompaniment of glossy skin Weir Mitchell noted the occurrence of "eczematous eruptions" which appeared as minute vesicles thickly scattered over the thin and tender cutis, or else occurred in successive crops of larger vesicles on the skin about the altered parts. Similar eruptions are observed rarely in the absence of causalgia and glossy skin. Keratoses occasionally appear on the palm and sole, in median and sciatic nerve lesions respectively (Fig. 56).

Changes in the distribution and rate of growth of the hair are common. Loss of hair is seen commonly in cases of glossy

skin and causalgia. At times it occurs in other lesions. Hypertrichosis is common and the hair is long and fine. The hair changes do not follow the distribution of the injured nerve and

FIG. 58. Changes in nails following peripheral nerve injury.

are probably due to factors other than nerve injury. (Fig. 57.)

A decreased rate of growth of the nails is, as pointed out by Head, due to immobility. Overgrowth is common in painful lesions and the nail increases in the long axis to become protuberant over a clubbed finger. Extreme lateral arching occurs and the bed is adherent to the nail so that the space between the nail and finger is destroyed. Transverse ridges, irregular hypertrophy and discoloration may appear. The nail is often pink in color, brittle and horny. At times ulcers appear at its base. Thickening of the nail pad is common. Whereas some of these changes are due to immobilization, some are the result of concomitant vascular lesions. (Fig. 58.)

During the time when the skin is insensitive to pain it is particularly liable to injury. So-called trophic ulcers occur only

during this period and occupy the insensitive area. They are produced usually by some injury, such as burning the finger with a match when a median nerve injury is present. Flicking

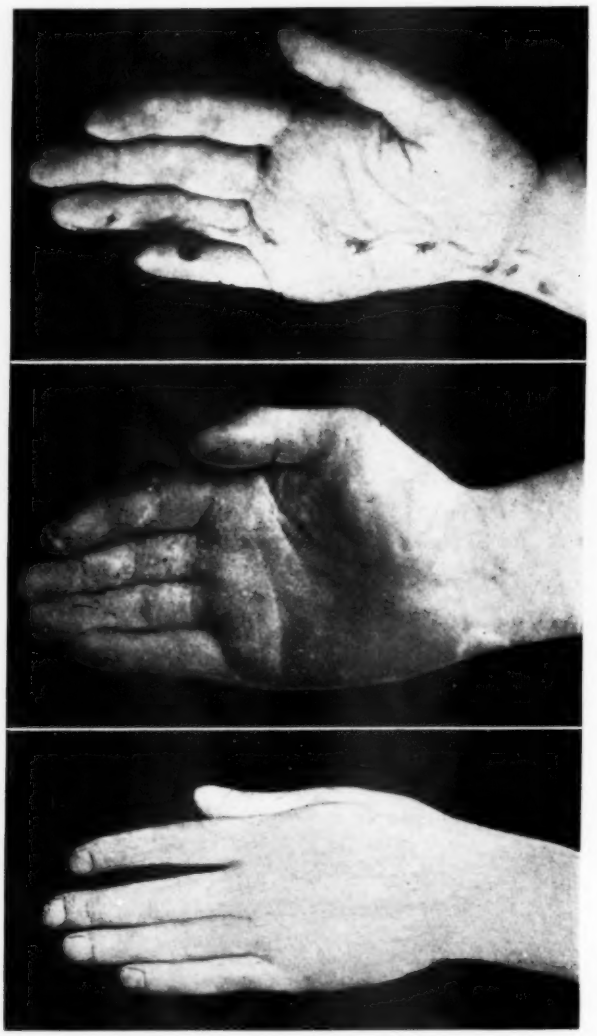


FIG. 59. Ulceration of index and little fingers in median and ulnar nerve lesions.

cigarette ashes with the little finger in ulnar nerve lesions or rubbing the heel with an ill-fitting shoe in sciatic nerve lesions are frequent etiologic factors. Relatively low temperatures may produce blisters when the skin is hypothermic. At times

they occur without known cause, appearing first as a blood blister. Healing is very slow because of repeated injury and the existent vasomotor changes, but otherwise the process of

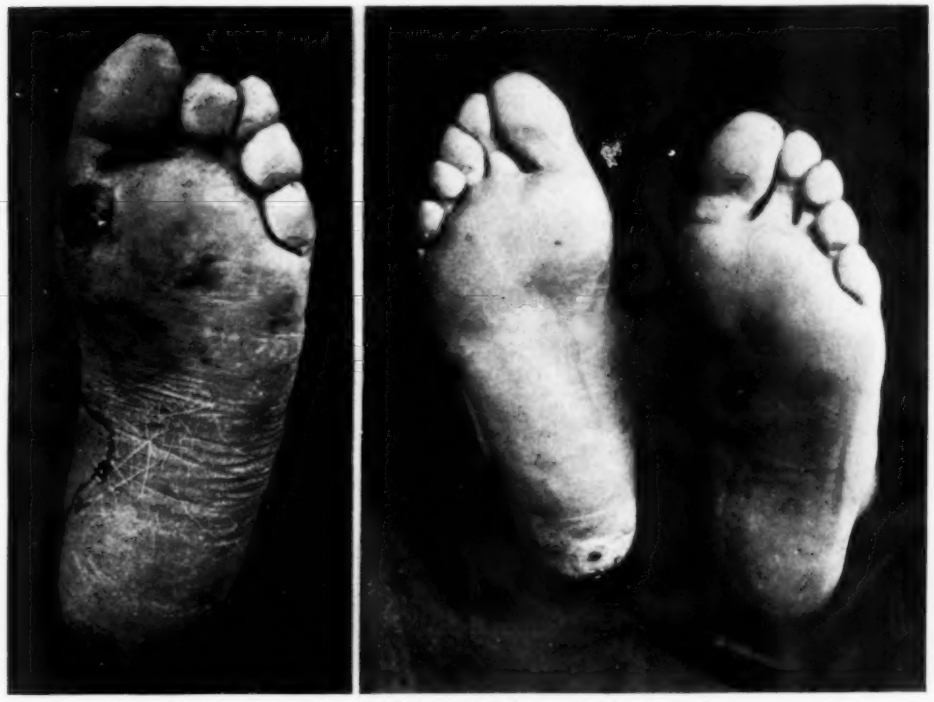


FIG. 60. Ulceration of heel and sole in sciatic nerve lesions.

healing resembles similar pathology in normal tissues. Infections are common and the ulcer burrows under the subcuticular tissues and at times affects the bony structures. Suppuration may occur, and a chronic sinus forms which continues to discharge a foul secretion. These ulcerations differ materially from those seen in vascular lesions where areas in which sensation is preserved are involved and massive ulceration and gangrene occur (Figs. 59, 60).

The changes in the subcutaneous tissues, such as edema, or subdermical, hard, inelastic induration, similar to chronic trophedema, are attributed rightly by Bénisty to vascular, or perhaps perivascular, lymphatic changes. Similarly, vascular lesions may produce fibrous degeneration or fibrosclerotic

changes in the flexor muscles of the fingers with retraction of their tendons. An appearance similar to Volkmann's contracture results.

Disturbances in secretion of sweat are commonly observed. Usually in complete lesions absence of sweat occurs and injections of pilocarpin fail to induce perspiration over the affected skin. Hyperhidrosis is common, particularly in partial lesions and at times in painful ones. Peculiar disturbances in the character of the sweat with putrid or sour odors occur infrequently. At times unpleasant odors may result from a maceration of the skin in painful lesions.

Chapter IX

EXAMINATION (*Continued*)

IX. Electrical Examination

The early hopes of neurologists and surgeons that a rapid electrical examination would serve to indicate the situation, nature and extent of a peripheral nerve lesion were quickly dissipated. Cases were found in which complete section of a nerve produced the electrical signs of a partial lesion, and indications of complete section were found in cases which presented a slight injury to the nerve. For a time electric diagnosis was discredited and later more carefully studied. As a result, it may be said that although alone it is not of absolute value, together with other signs and symptoms it is of certain diagnostic and prognostic assistance.

Reaction of Degeneration: Normal nerves and muscles with an intact nerve supply react by constant, characteristic contractions of the muscles when stimulated by faradic and galvanic currents. When a nerve or muscle is stimulated by a single stimulus, make or break, there is produced a sudden rapid contraction which spreads so rapidly that to all intents and purposes a whole muscle contracts, and as quickly relaxes. If, however, the stimuli follow one another at regular and, to a certain degree, rapid intervals, as with the faradic current, a tetanic contraction of the muscle occurs. When stimulated by a constant current certain electric changes are produced in a nerve which differ with the intensity of the current, the polarity of the active electrode and the make or break type of stimulation. As a result, a law of the normal contraction in man may be formulated. The reactions of muscles follow closely those of a nerve. This law may be expressed by the formula: Kathodal Closure Contracture (KCC) > Anodal Closure Contracture (ACC) > Anodal Opening Contracture (AOC) > Kathodal Opening Contracture (KOC).(KCC > ACC > AOC > KOC).

A muscle is stimulated most readily through its nerve supply and contraction will be produced most readily when the stimulus is applied over the point of entry of a nerve, that is, over the motor point of the muscle.

When a nerve has been severed certain changes occur in reaction to electrical stimulation which, grouped together, constitute the "reaction of degeneration" (D.R.). These changes may be described as quantitative, qualitative, modal and polar.

The excitability of the nerve for faradic and galvanic current is abolished. The muscle loses its excitability for the faradic current (qualitative). In the early stages, for about the first two weeks, the muscle is hyperexcitable to galvanism, and later hypoexcitability gradually supervenes so that much greater quantities of current are necessary to produce a contraction (quantitative). The character of the response is entirely altered. The muscle having lost its fibrillary element, which contracts with a brisk twitch, and which can be stimulated by a faradic shock, now retains only its sarcoplasm, which contracts slowly and can be stimulated only by the galvanic current. The quick twitch is replaced by a slow contraction which spreads gradually along the fibers in a wave and the relaxation is similarly retarded (modal). Whereas normally the polar formula is KCC > ACC the degenerated muscle reacts in inverse order to galvanic stimulation, ACC > KCC (polar). In practice, polar inversion is not always present in a degenerated muscle and under certain conditions, such as chilling, may be found in normal muscles. It has been found that only the make stimulus of the kathode is effective and that the anode at its make is the indifferent pole. When a contraction occurs upon a make stimulus of the anode it is probably due to a stimulation by the virtual kathode at the point of exit on the opposite side of the muscle. Such virtual kathodes are not sufficiently under control to give reliable results, and polar inversion is inconstant and unreliable as a sign of reaction of degeneration. Failure of reaction of the muscle to faradism usually develops

after two weeks of progressive diminution. It has been found that in some instances when a proven complete anatomic lesion of the nerve has existed for a long time muscles supplied distally still respond to direct (not percutaneous) faradic stimulation.

The most valuable indication of the reaction of degeneration is the slow character of the muscle contraction. Unless graphically recorded by myograms, sluggishness of contraction requires some experience for its estimation, but commonly the appearances are unmistakable.

At times only a partial reaction of degeneration is found when the lesion is less severe. This often consists of only a diminution of faradic and galvanic excitability of the nerve or only a diminution of faradic excitability of the muscle and sluggish contraction or a rapid contraction and sluggish relaxation of muscle when stimulated by the galvanic current. Although evidence of a complete reaction of degeneration some months after injury may be accepted as indicating a severe nerve lesion, physiologic interruption cannot be differentiated from anatomic section by electrical examination. Complete reaction of degeneration cannot be used alone as an indication of an irreparable lesion. As time progresses in complete lesions the excitability of the muscle to galvanism diminishes and finally, from twelve to twenty-four months after the injury, completely disappears.

The reaction of degeneration is ushered in by an initial phase which is characterized by a progressive diminution of faradic excitability of the muscle, galvanic hyperexcitability of the muscle and a gradual increase of sluggishness of contraction of the muscle. This phase lasts from ten to fourteen days.

Whereas normally a muscle is most readily stimulated at its motor point, when degenerated the muscle responds to stimulation not through the medium of its nerve but directly through its fibers (Fig. 61). As a result, the muscle responds best to a current which passes longitudinally through its substance.

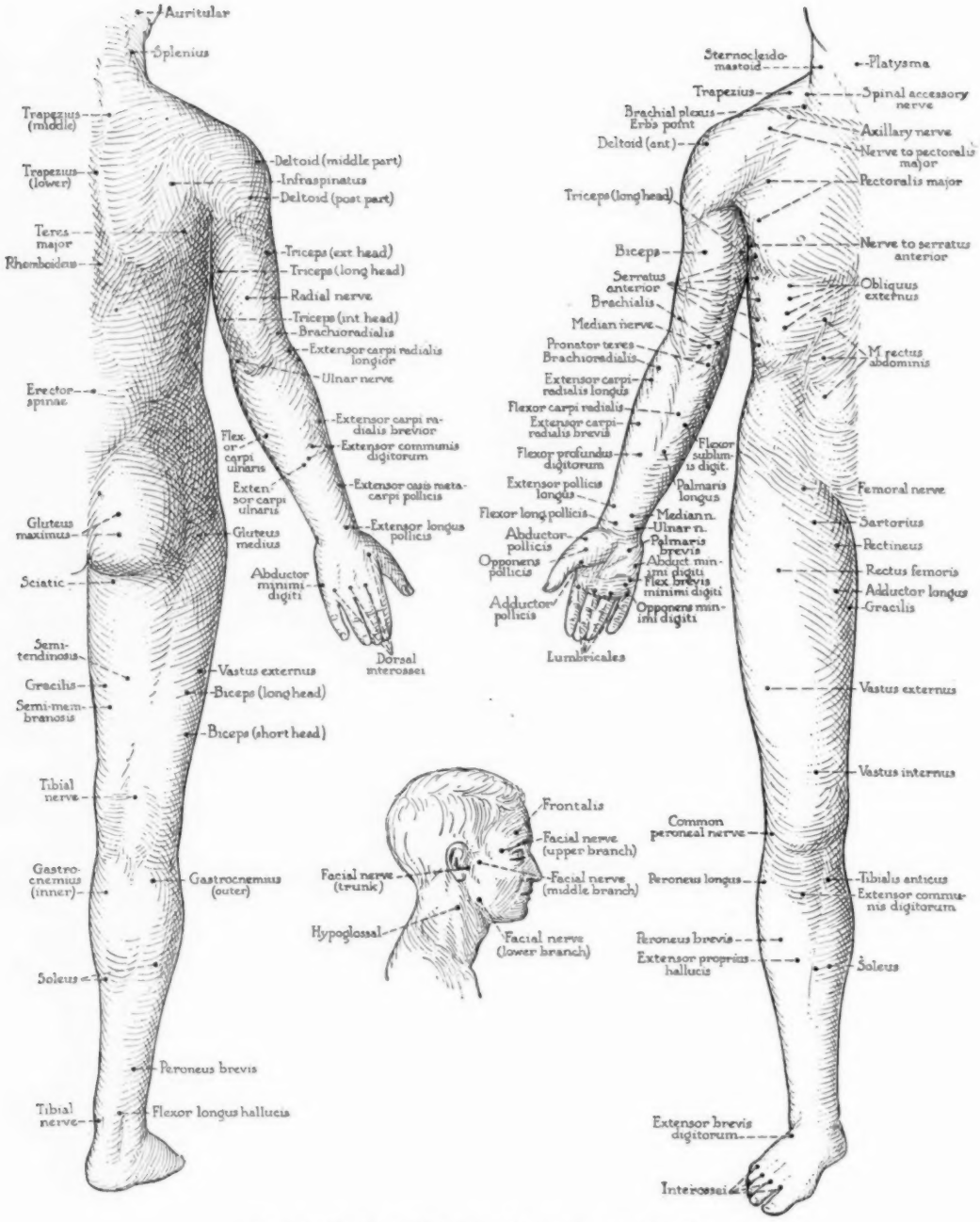


FIG. 61. Motor points for electrical examination.

This reaction, to which Ghilarducci gave the name of "reaction at a distance," is demonstrated by placing an indifferent electrode on the sternum or back of the neck and the active electrode not on the muscle itself but at a point *distal* to its tendon. The muscular contractions predominate at the closure of the negative pole and are elicited with currents three to four times weaker than those required to make the muscle contract with direct excitation. They are said to persist long after every trace of electrical excitability to direct stimulation has disappeared. Many clinicians place the active electrode on the lowest point of the muscle, near its tendon, and describe the reaction as the longitudinal reaction (Huet). Although the "reaction at a distance" is a constant and characteristic finding soon after injury, we have not found it to be of any value in lesions of more than six months' duration. The excitability has so diminished by this time that diffusion occurs into unparalyzed muscles when an attempt is made to produce a contraction by the use of increasingly larger amounts of current.

METHOD OF EXAMINATION: The apparatus necessary is found combined in many types of wall plates and tables. Faradic current may be obtained from an induction coil with two dry cells, and galvanic current from a battery of thirty-two elements which are capable of giving a current of 20 to 30 ma. (Fig. 62). When available, the most convenient source of electricity is that from an electric light current which furnishes direct current. When alternating current is used it must be converted into direct by a rectifier. A rheostat is necessary and a milliampere meter should be in the circuit. The active electrode for galvanic stimulation should be a small, button-shaped one with a pad about 2 cm. thick. The handle should be equipped with an interrupter. The indifferent electrode should be large (7 × 7 cm.).

Examination with the faradic current may be conducted by the unipolar or bipolar method. In the unipolar method, the pads of the indifferent electrode, moistened with normal salt

solution, should be placed upon the sternum, lumbar region or opposite extremity. The active electrode which is also moistened is then employed in searching out and stimulating muscles

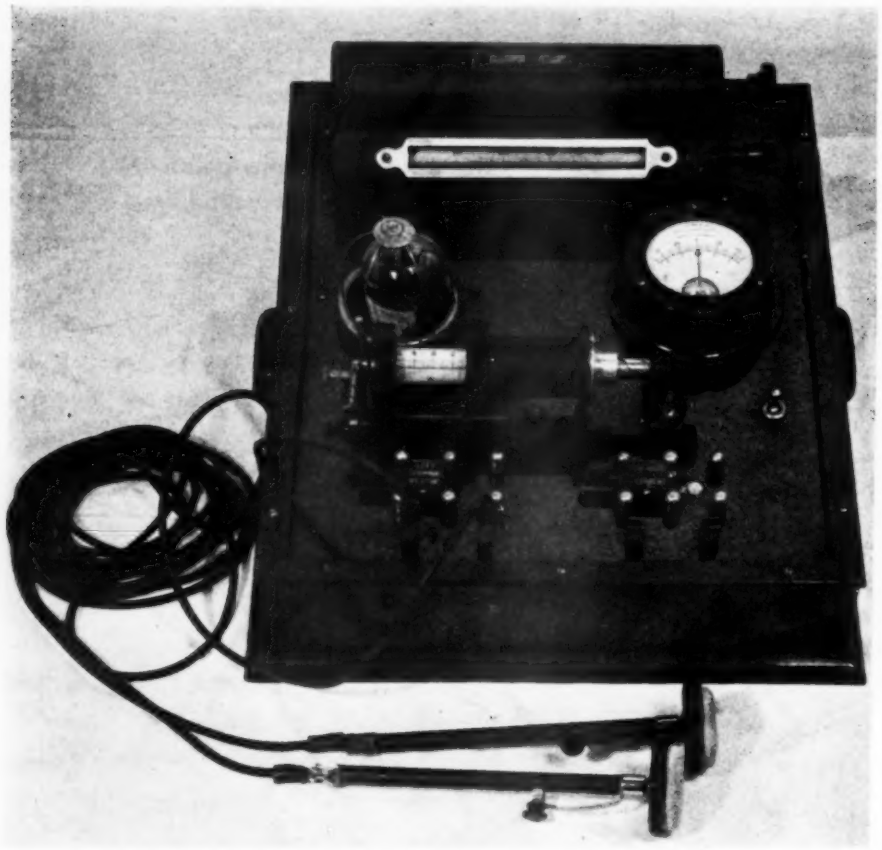


FIG. 62. Wall plate apparatus for making electrical examinations.

and nerves. It is usually found that such large amounts of current are necessary to produce contractions in paralyzed muscles that diffusion of current occurs into unparalyzed muscles and conceals any possible contraction of the affected ones. It is better, therefore, to use two small electrodes, both placed on the muscle to be investigated. This is the bipolar method. For examination with galvanism the unipolar method is usually satisfactory.

All the apparatus should be within easy reach of the examiner. The patient should lie or be seated in a good light, with the muscles perfectly relaxed. Contraction of muscles may be recognized from movement of the segments about joints, or by direct observation and palpation of the muscles when stimulated. If the movement of part of an extremity is to be used as an index of contraction, the part should be supported in that position which places the muscle in its most effective position. For example, in testing the extensor communis digitorum the proximal phalanges should be extended passively to the level of the dorsum of the hand. In testing the dorsal interossei the palm should rest flatly upon a table. As a general rule the muscle should not be in a position of complete elongation but should be midway between its lengthened and shortened states. It must be remembered that when fibrosis, shortening and joint changes render conditions suitable for supplementary motility, contraction of the muscles which produce such trick movements voluntarily may produce them when stimulated electrically. For example, stimulation and the resulting contraction of the flexors of the fingers may produce an extension of the wrist in radial nerve lesions. The contraction of a muscle can more readily be felt when it is completely relaxed and unstretched. When the contractions of the muscles of the uninjured extremity are used as an index of comparison with those of the injured one care must be taken to insure a similar distance between the electrodes.

Repeated stimulation over an area of skin reduces the resistance and produces a stronger stimulation, and in using the faradic current one should have this in mind. In using galvanism the milliampere meter gives a relative indication of the strength of the current.

Often contractions resulting from electrical stimulation may enable one to detect the earliest voluntary motion. The patient may be able to maintain a position produced by the contraction of muscles electrically stimulated for a short time

when he is unable voluntarily to produce that motion or to maintain such a position passively produced.

Electrical examination likewise is often valuable to differentiate loss of motion due to severed tendons from paralysis. In the former galvanic stimulation followed by a good contraction in the muscle fails to produce a movement of that segment to which the tendon is attached.

CHRONAXIE: An electric stimulus must reach a certain intensity before it will result in the contraction of a muscle. This minimal current, however, must be prolonged for a certain length of time to produce a response. At "infinite duration" there is a minimum strength below which no contractions occur (rheobasic voltage). As the duration is decreased the strength must be increased until a point is reached where, no matter how strong the current, no contractions follow. The minimal duration of current necessary to produce a contraction with twice the rheobasic voltage has been designated empirically as the chronaxie of the tissue. The chronaxie of a human muscle with an intact nerve supply has been found to be 0.00016, whereas that of one whose muscle has degenerated is about 0.01. It was hoped that measurements of the chronaxie would furnish accurate information of diagnostic and prognostic value in peripheral nerve injuries. Although they have served to give precise measurement of the functional value of nerves and muscles in physiology, because of the inaccessibility of accurate instruments and the unreliability of certain others, few data are available which permit of critical judgment of its clinical value. When measured by the condenser system of Lewis Jones, it has failed to impress the American investigators with its reliability. More accurate methods, such as the Lucas pendulum, Lapicque's chronaximeter, Strohl's érgersimètre and Sachs' and Malone's chronomyometer have appeared to give accurate information in their several investigator's hands. It is possible that they may lead to profitable clinical investigations in the future.

Chapter X

EXAMINATION (*Continued*)

x. Reflexes

In general, disturbances of reflexes are not significant in relation to the diagnosis and prognosis of peripheral nerve lesions, as they are in disease or injury of the central nervous system. Frequently, however, they are of considerable importance. Naturally, they are very useful in diagnosis and prognosis of lesions of the cauda equina.

The most important deep reflexes are the Achilles' jerk, the knee-jerk, the wrist-jerk or styloradial reflex, the ulnar pronator reflex, the biceps-jerk and the triceps-jerk.

The muscles of the extremity whose reflexes are being studied must be completely relaxed. When a tendon reflex is to be elicited that tendon must be stretched passively to a moderate degree. In examining for deep reflexes it is important to note not only their presence but differences in reaction and degree of stimulation necessary to elicit them as compared to the normal side. Often a slight reaction may be felt in the contraction of muscle insufficient to produce a visible movement of segments about a joint. Great care must be exercised to avoid confusing an idiomuscular contraction with a true deep reflex. An idiomuscular contraction is obtained by striking the mass of muscle itself, preferably at its motor point. Frequently, during the early stage of reaction of degeneration, this reaction is increased and persists for a long time after a peripheral nerve injury. Ankylosis of joints and shortening, infiltration and fibrosis of muscles and fasciae frequently mask a deep reflex. Their presence should always be noted and properly evaluated in relation to the examination.

The Achilles' jerk is mediated through a reflex arc which is represented by the first and second sacral segments. It may be elicited by striking the tendon, which has been placed on tension by passive dorsal flexion of the foot, while the patient lies

in bed with the thigh and leg semiflexed, outwardly rotated and relaxed. It may be elicited more advantageously by striking the tendon similarly stretched with the patient kneeling on a chair and resting firmly upon the tibiae, with the muscles relaxed completely.

The knee-jerk, whose reflex arc is mediated through the third and fourth lumbar segments, is commonly obtained by striking the passively stretched patellar tendon. It is preferable to examine the patient in a recumbent position, the thigh and leg being semiflexed, outwardly rotated, and supported by one of the examiner's hands. Likewise the reflex may be elicited by pressing the patellar tendon downward with a forefinger, putting the quadriceps muscle upon a stretch and then striking the finger with a percussion hammer. Less satisfactory methods are to strike the patellar tendon with the patient sitting in a chair with the feet resting upon the floor, or with the leg to be examined crossed over the opposite one. At times complete relaxation is difficult to obtain and some method of "reinforcement" may be used. The patient, looking upward, may lock the hands together, pulling them one against the other, upon the count of three when the examiner strikes the tendon with the hammer. Or, the examiner may grasp the quadriceps of the patient who sits in a chair with his soles flat upon the floor. The patient then grasps the arm of the examiner and squeezes it firmly when commanded, at which moment the examiner strikes the tendon.

The styloradial reflex, or wrist-jerk, mediated through the fifth and sixth cervical segments is elicited by striking the styloradial process. The forearm should be semiflexed and midway between pronation and supination, with the muscles all relaxed. This reflex evokes a contraction of the biceps, the brachialis anticus, the supinator longus and, at times, some fibers of the deltoid.

The ulnar-pronator reflex, innervated by the seventh cervical segment, is evoked by striking the posterior surface of the styloid process of the ulna, the upper extremity being in a

position similar to that just described. It produces a movement of pronation of the wrist.

The triceps-jerk, mediated through the seventh and eighth cervical segments, is elicited best by supporting the upper extremity with the arm horizontal and the forearm semiflexed, the muscles being completely relaxed. Then after locating it by palpation the triceps tendon is struck with the hammer. This produces a contraction of the triceps and an extension of the forearm.

The biceps-jerk is represented in the fifth and sixth cervical segments. It is elicited by striking the bicipital tendon through the examiner's finger or a pleximeter placed over the tendon with the upper extremity supported and the forearm semi-extended.

Cutaneous reflexes are affected chiefly by lesions of the cauda equina and of the nerves of the lower extremities. The plantar reflex is evoked by stroking the outer edge of the sole from the heel to the toes. At times it may be obtained better by stroking the middle or inner side. Normally, plantar flexion of all the toes results. The cremasteric reflex is affected most frequently in injuries of the spine which produce cauda equina lesions, and injury to the adjacent emerging roots. The cremasteric reflex is obtained by stroking or compressing the inner aspect of the thigh. Care must be exercised to differentiate the slow, vermicular contraction of the dartos muscle from a real reflex, which produces a sharp retraction of the testicles toward the inguinal canals. The abdominal reflexes, upper and lower, consist of a brisk contraction of the muscles when the skin over the abdominal wall is stroked from behind forward. At times the gluteal reflex is absent in high lesions of the sciatic nerve. This consists of a contraction of the glutei when the skin over the buttocks is stroked.

Chapter XI

DIAGNOSIS

Differential Diagnosis

The diagnosis of complete lesions of peripheral nerves is essentially simple. Other causes of loss of motor function such as severed tendons, fractures, dislocations, inflammatory reactions, fibrosis and ischemic paralysis are differentiated readily by the absence of the combination of motor and sensory loss and change in electrical excitability. The electrical reaction is particularly valuable in the differentiation of severed or adherent tendons. When the injury is distal to the point of the exit of a nerve branch to that particular muscle the diagnosis is self-evident and is further confirmed by the contraction of the muscle upon faradic stimulation, without appropriate movement of the segment normally moved by that muscle. When the injury is above or at the level, stimulation below the lesion will produce movement of the segment and stimulation above the lesion will produce contraction of the muscle and no movement of the segment.

At times when an injury produces, among other things, a loss of function of a particular nerve, other changes such as hemorrhage, fracture, edema or inflammation may produce signs and symptoms which may be misinterpreted as an injury to an additional nerve. These signs and symptoms never produce the complete syndrome of a nerve injury and are fleeting in nature.

In general, when a particular peripheral nerve is severely injured there is a paralysis of a particular group of muscles, a loss of sensation over a certain constant area of skin and an inability to perform specific movements. In partial lesions of some nerves, such as the radial, there may be little or no sensory loss and a dissociated paralysis may lead to some difficulty in diagnosis. Electrical examination then is of great service and

when evidence of the reaction of degeneration is found a diagnosis of a peripheral nerve lesion is evident.

Injuries of the central nervous system usually afford little difficulty in differential diagnosis. In lesions of the corticospinal tract the signs of an upper motor neuron injury rapidly determine the diagnosis. These signs are spastic paralysis, increased deep reflexes, diminished superficial reflexes, presence of pathologic reflexes, such as the Babinski phenomenon and absence of marked atrophy, or the reaction of degeneration.

Unilateral lesions of the spinal cord, with concomitant brachial plexus injury, at times present a picture, when seen some time after injury, which leads to failure of recognition of the brachial plexus lesion. In such cases the paralysis of the upper extremity may be attributed wrongly to injury of the anterior roots or anterior horn cells. Usually the absence of a segmental character of the loss of motion and sensation points to the correct diagnosis. This will be dealt with further in the chapter on the Brachial Plexus.

Intramedullary spinal cord lesions, although rare, are differentiated by the segmental distribution of paralysis and the dissociated sensory loss. For example, there may be a loss of heat, cold and pain sense and preservation of touch.

Lesions of the cauda equina, when unilateral, may offer some difficulty. Disturbance of rectal and bladder reflexes, and sensory loss in the saddle area, which involves the third, fourth and fifth sacral segments, serve to localize the lesion accurately.

An organic lesion is characterized by the production of certain constant and expected signs and symptoms, and only those. A paralysis of functional nature such as that found in hysteria, is characterized by some signs and symptoms which could not be the result of a lesion which produces other signs and symptoms. In addition certain signs and symptoms which would inevitably result from such a lesion are usually absent.

The disturbances of motility in a functional paralysis are characterized by their variability. The patient may profess to

be unable to extend the hand upon command and yet be observed to extend it to a slight degree in performing some other required function. Or, although no contraction in the extensors may occur upon request, in the course of the examination the hand may be passively extended and remain in that position. The deformity which is present never follows the physical laws of loss of function of particular muscles. Often a contraction may be found in the supposedly paralyzed muscles. Thus in a supposed inability to extend the wrist or contract the extensors, the hand may be held fixed in a position of semi-extension, although the wrist may be passively moved freely in all directions. The position of extension will then vary in degree according to the position in which it is passively placed, or it may again assume such a position after the hand is passively flexed. The position produced by the contraction or deformity cannot be explained by the paralysis of any group of muscles supplied by one or more peripheral nerves, neither can it be explained by the unopposed action of other groups of muscles supplied by other specific nerves. Thus in a supposed inability to move any muscle of the lower extremity, the leg, foot and toes may be held rigidly in extension. Or, in the case of an inability to move the fingers, the fingers may be flexed at the proximal and extended at the distal phalanges. The loss of function includes certain muscles which could not be affected when only a certain nerve was injured. On the other hand, there is movement of other muscles which would be paralyzed if such a nerve were actually injured. Thus, in an inability to flex the wrist or any of the fingers the thumb may be opposed to the little finger (median) and a piece of paper may be grasped tightly between the thumb and index finger (ulnar). Manifestly this is a combination which could not occur as the result of a combined ulnar and median nerve palsy which would appear to be present in view of the loss of motion in the wrist and fingers.

When sensation is lost in a functional lesion the area of anesthesia never follows a peripheral or even segmental dis-

tribution. It is more often geometric in distribution such as glove and stocking anesthesia on the volar or dorsal surfaces. However, when muscles supplying flexion are supposedly paralyzed as in a combined median and ulnar nerve lesion, and the entire palm is anesthetic, the dorsal surface of the distal phalanges of the index and middle fingers may have quite normal sensation. Moreover, the borders of the area of sensory loss constantly shift during examinations conducted only a few minutes apart. When a patient complains of spontaneous pain and tenderness on pressure, examination for tactile sensation may develop an anesthesia, then an analgesia and finally pressure of considerable force may be exerted without evoking sensation. Often the patient may be instructed to say "yes" immediately when he feels a pin prick and "no" when he does not feel it. Under such a condition the patient may reply "no" with absolute chronological accuracy when the stimulus is applied to a professedly completely anesthetic and analgesic zone. The borders of the areas to tenderness or pressure shift with each rapidly succeeding examination. This is well demonstrated by making simultaneous pressure with two fingers, one over the point of supposed tenderness and the other a short distance away. No areas of overlap are found, and usually sensation of all modalities is lost over the same areas. Peculiar dissociations of sensory loss may at times be found. Thus, a patient may profess to be unable to feel pain but to distinguish heat and cold.

Reactions of the muscles to faradism and galvanism in a functional paralysis are always normal except when the extremity shows vasomotor change. Then a quantitative diminution may be present. The reaction of degeneration is never present. Trophic ulcers are not found, although cyanosis and hyperhidrosis of the palm and an apparent increased nail growth are common. When muscle atrophy is present it is general in character and does not select certain muscles.

The occurrence of functional paralysis, spasms and contractures varied in different armies in the war to an astounding

degree. Cases which simulated lesions of the peripheral nerves were exceedingy rare in our material, which was gathered from four large base hospitals in France (Base Hospitals 24, 28, 13 and 3), and a general hospital (U. S. General Hospital 28) in the United States. A considerable number of cases of "barracks back" (camptocormia), astasia abasia, hysterical paraplegia and hemiplegia, mutism, aphonia, myoclonias, stuttering and tremors were seen, but so few cases of involvement of only one extremity came to our attention as to be notable.

Paralysis limited to one anatomical region or group of muscles with wounds at a distance was seen commonly among the French forces. It is exceedingly likely that the relatively short duration of time our troops participated in the war, the rapid movement from one to another hospital, the frequently required redressing and inspection of wounds and the prevention of prolonged uninterrupted immobilization and monotonous hospitalization were factors in the prevention of the development of these functional disabilities.

Not only were well-recognized examples of hysterical paralysis and contracture of upper and lower extremities found by the allies, but many of the French observers separated from the total material a group which Babinski and Froment designated as reflex nervous disturbances, and later as physiopathic affections. These contractures or paretic conditions which occur at a distance from a wound have this common characteristic; they are sharply localized in a segment of a limb or in certain muscular groups, commonly of the extremities. Though the tendon and bone reflexes may not be modified to any extent, there is generally a condition of mechanical hyperexcitability of the muscles of the affected limb, and a corresponding hyperexcitability to faradic and galvanic currents, with rapid fusion of the contractions. These modifications of excitability are partly the result of the lowered temperature of the extremity. They improve upon the application of heat and are exaggerated by cold. The contractures disappear under ether anesthesia, but at times only under deep narcosis.

Vasomotor disturbances are very frequent. A hand may show cyanosis, lowered temperature, diminished amplitude of the pulse, disturbances of sweat secretion, moisture, maceration of

FIG. 63. Contracture of fingers without injury to peripheral nerves of upper extremity. This is an example of the congealed hand (Meige) or a physiopathic affection (Babinski and Froment).

skin and decalcification of bone. This condition, also termed the congealed hand of Meige, acromyotonia by Sicard and paratonic paresis of Marie and Foix, resists all physiotherapeutic methods which ordinarily improve rigidities and contractures which result from osteo-articular and muscular lesions. Psychotherapy, in the hands of many, has proved equally ineffective. (Fig. 63.)

The pathogenesis of these affections has been very extensively discussed. Babinski and Froment, Léri, Roger and Guillain and A. Barré were the first to insist upon the necessity of distinguishing these disorders from hysteria. Babinski and Froment regard the lesion as being of a reflex character. By some the condition is regarded as due in some cases to irritation of the muscle by metal dust; in other cases, to irritation of a nerve by foreign bodies, or cicatricial fibrous tissue. By others it is thought to be the result of ischemic contraction or neuritis. Many attribute it chiefly to prolonged immobilization of the extremity. On the other hand, as has been pointed out by Claude and Lhermitte, and Roussy and Lhermitte, all the signs described by Babinski and Froment as characteristic

of reflex disorders may be found without any bodily wound, and at times they disappear under treatment by psychotherapy. It is sufficient for our purpose to note the occurrence of these disorders and to indicate the source of information concerning them in the event the necessity arises for their recognition, study and treatment.

Chapter XII

DIAGNOSIS (*Continued*)

1. Signs of Severe Nerve Injury

If it were possible to differentiate complete interruption of the function of a nerve due to section from that due to contusion or compression, an immediate decision could be reached for early surgical intervention. This would result in a marked increase of the recovery of function of injured nerves. However, in many instances this conclusion can be reached only after a period of observation of a number of months.

Many attempts have been made to discover a sign or a group of signs which would justify a rapid differential diagnosis between a complete anatomic section of a nerve and one in which complete loss of function is the result of a physiological interruption of the nerve fibers. Similarly, attempts have been made to differentiate those cases which have a complete loss of function and which are spontaneously recoverable from those which will not recover without surgical interference.

Some observers have thought it possible to distinguish several definite symptom-complexes. Thus, Mme. Dejerine and J. Mouzon have described the syndromes of interruption, of compression, of irritation, of dissociation and of recovery, each of which has a distinctive group of signs and symptoms. The syndrome of interruption, or anatomic section, is characterized by (1) complete paralysis of all muscles supplied by the nerve below the lesion; (2) complete absence of tonicity, as demonstrated by softness and flaccidity of the muscles, and by the position of the extremity at rest. For example, the wrist-drop of a radial nerve lesion, the ape hand (median), the irreducible claw hand (ulnar), the excessive varus equinus (peroneal), and the foot-drop of a sciatic nerve lesion are all characteristic deformities. Finally, they call attention to the absence of pain on pressure of the muscles supplied by the injured nerve. Of secondary importance are the abolition

of reflexes, exaggerated excitability of the muscle to mechanical stimulus, amyotrophy, certain other deformities such as dorsal swelling of the carpus or tarsus, complete reaction of degeneration in the paralyzed muscles, absence of any zone of hyperesthesia or paresthesia in the region supplied by the injured nerve, absence of pain on pressure applied to the nerve trunk below the lesion, and the topographic distribution of the changes in objective sensibility.

The syndrome of irritation as described by these authors includes the painful injuries of nerves whereas the syndrome of dissociation relates to partial nerve lesions which give rise to an incomplete paralysis.

Dejerine and Mouzon described the syndrome of compression as characterized by the same phenomena as those of interruption, but to a lesser degree. Of paramount importance is the presence of pain when the muscles and nerve trunks are subjected to pressure, and the lesser degree of impairment of objective sensibility. This latter consists generally of hyperesthesia. The syndrome of regeneration will be referred to in the chapter upon Nerve Regeneration.

If these syndromes had absolute diagnostic value the entire matter of surgical treatment would be simplified. Unfortunately, this is not the case and the artificial division of cases into these groups has not withstood the tests of critical investigation.

In accordance with Pitres and A. Bénisty, we feel that there is no way by which a complete loss of function due to anatomical interruption can be differentiated from the complete loss of function due to physiological interruption produced by compression. From a single examination, at a given time, we can determine only whether the loss of function is complete or incomplete. If it is complete we cannot tell whether or not it is due to anatomical interruption, nor can we predicate whether it will recover spontaneously or will require surgical treatment. Of course, if it is incomplete, anatomical division cannot be present except in the form of a lateral notch.

In a case of complete physiological interruption we may say that an anatomical section does not exist, only when a subsequent examination shows some return of function. No other sign or group of signs suffices. In general, the course of the clinical picture is much more important than any group of signs for the purpose of determining the severity of a lesion.

The various clinical signs which result from the complete interruption of a nerve have been given a different value and significance by different investigators. Each one has proposed a certain grouping of symptoms in the order of their supposed value and many have added certain signs of their own. The following signs are accepted in common by the majority: (1) complete paralysis of all muscles supplied by the nerve below the lesion; (2) complete reaction of degeneration; (3) rapid and extensive atrophy of the paralyzed muscles; (4) absence of pain on pressure applied to the nerve trunk below the lesion; (5) loss of objective sensibility in the supply of the affected nerve. Bénisty has included vasomotor and trophic disturbances, especially the decrease in the local temperature of the skin which covers the atrophic muscles. From our material, the following analysis, which assembles some of the material already described under separate heads, may be made:

Complete loss of all the functions of a nerve indicates a severe lesion and is interpreted as a complete physiological interruption of that nerve.

Total paralysis of all the muscles supplied by a nerve distal to a lesion cannot alone be used as an indication of the severity of that lesion. Particularly is this true of the radial nerve. Slight injuries of this nerve produce total paralysis.

Complete loss of sensation in the isolated supply of a nerve indicates and is interpreted as complete physiological interruption of sensation.

Only when sensation is present in the isolated supply of a nerve can the lesion be considered as a partial one. The area of the isolated supply to pin prick of various nerves is the area

in which no overlapping occurs and is described in the chapter on Nerve Overlap. The area of analgesia to pinching corresponds to the area of the isolated supply of a nerve to pin prick. In our opinion this is an excellent indication of a severe nerve lesion.

Regarding the electrical changes demonstrated by the methods personally employed, namely, faradic and galvanic stimulation, it may be said that the complete reaction of degeneration is always present in a severe lesion. However, it does not indicate an irreparable lesion. A progressive increase in the signs of the reaction of degeneration speaks for a lesion which will not recover spontaneously. Of all the changes to electrical stimulation the slowness of the muscular contraction was the only constant phenomenon which could be satisfactorily employed to determine the reaction of degeneration. Polar changes were inconstant. Of course, it may be expected that the response to faradism would be absent frequently, even in partial lesions. Especially is this true of cases which require more than four months for recovery. Although electrical examinations afforded no means whereby a differentiation between anatomical and physiological interruption could be made in the cases observed within a year following injury, it must be remembered that frequently after this period, and always after 100 weeks, irreparable lesions show complete loss of response to any form of electrical stimulation. The longitudinal reaction did not prove to be of any particular diagnostic value.

Rapid and extensive atrophy of the paralyzed muscles may be interpreted to mean a severe lesion, with a number of reservations. Regardless of their severity, ulnar nerve lesions as a rule show extensive atrophy. Atrophy is of service in denoting the severity of a lesion only when it is present soon after injury. The amount of atrophy observed some months after injury is not commensurate with the severity of the lesion, nor is absence of demonstrable atrophy an indication of a spontaneously reparable lesion.

Absence of pain when the trunk of the nerve is subjected to pressure below the seat of the lesion was demonstrable in many severe lesions, but quite a number of recoverable lesions showed this analgesia as well. On the other hand, not a few irrecoverable lesions showed the preservation of pain to such pressure. Only the ulnar, radial and peroneal nerves are suitable for isolated pressure upon their trunks and this only in such cases in which the injury is proximal to their superficial positions. The danger of producing pain by pressure upon adjacent structures is too great to make this a universally diagnostic phenomenon of certain value.

In agreement with Meige and Pitres, absence of any pain on pressure of the muscles which are paralyzed was found a very unreliable sign. In fact, it was found that in a large number of cases tenderness to pressure was more marked on the injured side. Probably it could be attributed in some cases to the injury of other tissues; in others, to supplementary supply of sensation to the paralyzed muscle by adjacent nerves.

We do not feel that the absence of hyperesthesia in the area supplied by an injured nerve is an indication of the severity of the lesion. As a matter of fact, it is not uncommon to find hyperesthesia in the presence of a completely interrupted nerve when sensation to pin prick has returned as the result of nerve overlap.

When tone was measured by a tonometer, it was found that only for a short time after an injury of a peripheral nerve was the loss of tone any indication of the severity of the lesion. Even then the loss of the tone represented only a reflection of the general loss of function. The difference in millimeters of mercury was expressed in the ratio of from 160 to 180 in normal muscle to 40 to 60 in the paralyzed ones. In a very few weeks, infiltration, fibrosis and other changes in the muscles and tendons vitiated whatever significance loss of tone might have.

Too little is known of the nature of trophic disturbances to enable us to employ them profitably in interpreting the severity of the lesion. When protopathic sensibility was lost trophic

ulcers were likely to occur. When an extremity was immobilized, the growth of nails ceased. When an extremity was protected by a dressing hypertrichosis was at times observed. Generalized atrophy of the bones indicated only disuse. In other words, the trophic disturbances can be employed as an indication of the severity of the nerve lesion only when they are associated with more important signs.

We consider that when they exist together the complete paralysis of all muscles supplied by a nerve below the level of the lesion, the complete loss of sensation over the accepted sensory distribution of the isolated supply of a nerve and the complete reaction of degeneration are the only reliable signs of a complete interruption of function of a peripheral nerve. Whether this interruption is due to anatomic section or not cannot be determined. Whether the lesion may recover spontaneously can be told only from the evidence of some return of function in motion, sensation or electrical excitability as may be determined by continued examinations over a period of time.

Chapter XIII

DIAGNOSIS (*Continued*)

II. Recovery of Function

The signs of regeneration of a nerve are the manifestations of recovery of function. Among these are return of sensation, both subjective and objective, disappearance of the reaction of degeneration, return of motion, increase of tone and disappearance of muscle atrophy.

These manifestations differ in appearance and rate of return in relation to the pathology of the nerve and according to whether recovery is spontaneous or is consequent to surgical intervention. They are dependent upon the condition of the neuraxons. If descending degeneration has been slight or absent and the nerve recovers spontaneously and rapidly the clinical course of the symptoms of recovery of function may be quite different from that seen if resection and suture have been performed. If little or no degeneration has followed, but a complete physiological interruption has existed for a long time, perhaps because of a constricting band of scar tissue, surgical relief of this condition may be followed by symptoms of regeneration similar in character to those observed in lesions which rapidly recover spontaneously. If descending degeneration is severe or complete and conditions are such that the lesion recovers with no surgical interference, the course of recovery will be very similar to that observed which follows nerve suture.

Many cases of complete physiological interruption of a nerve showed their first sign of regeneration at such a time as one would expect it to occur were the nerve divided at the time of injury and sutured. From this time onward the signs of regeneration progressed exactly as they would in a sutured nerve. It is reasonable to assume that in this type of severe lesion complete descending degeneration had occurred and conditions permitted the regeneration of the axons. Evidence

of regeneration first appeared in from the eighth to ninth month, and it was noticeable that a considerable number of men wounded at about the same time all began to improve together.

The order in which the signs of regeneration appear has been given by Bénisty as follows: (1) sensory regeneration, consisting of pain when the skin is pinched, pain when the nerve is pressed below the lesion, formication on pressure of the nerve and spontaneous aching in certain muscles; (2) arrest of muscle atrophy and return of tonicity; (3) in some cases return of faradic contractility; (4) disappearance of objective sensory disturbances; and (5) return of voluntary movements.

Recovery of Sensation: Rapidly and spontaneously recovering lesions showed two characteristics. First, in agreement with others (Sherren), we found that such lesions do not show the dissociation of sensation to which reference has been made. In these cases little or no sensibility to pin prick returned before tactile sensation. Both forms of sensation are absent and return together. Second, the return of function did not adhere to any definite rate of progression, either as to sensation or motion, and often all the muscles innervated by a nerve regained their function suddenly, irrespective of their distance from the lesion. Painful sensation evoked by pinching the skin is one of the earliest manifestations of recovery, and considerable valuable information is obtained by this method, as has been pointed out by André-Thomas and Babinski.

From an examination of 150 records which showed loss of sensation to pinching we found that when a single nerve is severed and the area of skin which it supplies is surrounded by skin supplied by intact nerves, no loss of sensation to pinching is found. Usually no loss to pinching could be found in severe lesions of the peroneal nerve, or in severe lesions of the radial nerve. Nerves which supply the distal portions of the extremities, as the ulnar and median, when severed showed loss to pinching. In all complete lesions of the ulnar nerve loss to pinching occurred in the distal phalanges of the little finger.

Only in recovering lesions is there no loss to pinching, and partial loss is found in partial lesions. In severe lesions of the median nerve loss to pinching occurred in the index and middle fingers; in recovering and partial lesions loss to pinching may be observed in one or the other finger only. When this is true, sensibility to touch and pain is only partially destroyed. When no loss to pinching was found the lesion was partial and was recovering. In combined section of the ulnar and median nerves loss of sensation to pinching was found in the distal phalanges of the four fingers. One or another of the fingers showed preservation of sensation in partial lesions, and were accompanied by similar partial involvement of tactile and pain sensibilities. In section of the sciatic nerve loss of sensation to pinching was found in the isolated supply of this nerve to deep sensation. No loss to pinching occurred in recovering lesions. When the peroneal portion of this nerve alone was severely injured, some loss to pinching was observed in the sensory area of the peroneal nerve.

These observations would permit one to select severe lesions rapidly when it is necessary to examine a large number of cases hurriedly. However, the same precautions must be observed relative to examination by pinching as by other methods of stimulation. The return of this sensibility is valuable as a sign of recovery only when it returns in areas in which there is no overlap of adjacent intact nerves. Attention has been called to its appearance in small, circumscribed spots. From our observation, these spots which later combine occur chiefly in areas of overlap and are not due to regeneration. However, all observers feel that this sign precedes the appearance of formication noted by Létiévant and described by Tinel.

Formication of distal tingling on pressure (*Tinel's sign*) is described as a tingling or other paresthesia in the part supplied by a peripheral nerve when the site of the injury is percussed, and later when the nerve is percussed at progressive distances distal to the injury. It has been said to give valuable early

information as to the process of regeneration. As long as the formication is elicited only from the site of injury the sign is valueless because cicatricial topoparesthesia is a constant accompaniment of neuronal formation. When repeated and successive examinations, with palpation and pressure on the nerve distal to the injury, give rise to formication at increasing distances from the point of injury with certain precautions it is a possible indication that regeneration is occurring.

The reaction is commonly obtained first at the site of injury as early as the twentieth day, but generally between the fourth and sixth weeks. By the thirtieth day it may be obtained 2 cm. below the lesion; by the sixtieth, 5 cm. and upon the ninetieth, 9.5 cm. below the lesion. The rate of progression varies in different cases. MacDonald has pointed out that the downward progression occurs at a rate of 1–2 mm. a day, and that after the expiration of 100 days the site of injury is no longer irritable. At the expiration of another 100 days the irritable portion of the first period loses its irritability. It is suggested that the percussion be made from the periphery proximal because if formication is once produced it may persist for some time and lead to misinterpretations.

American observers have not been in general agreement as to its precise value. Our personal experience would lead us to discredit it as a reliable index of regeneration. If the sign is elicited by palpation alone some value may be attached to it. If it is elicited by percussion but little value can be ascribed to it since connective waves of motion are transmitted to the newly formed curling axons at the site of the neuroma. As an example of its unreliability, we failed to elicit it in 7 of 50 recovering cases. In 8 cases the formication could be elicited from a point only a short distance from the site of injury. The sign was elicited completely in 5 per cent of 50 complete interruptions and was absent entirely in only seven. The variance of technique and interpretation in the hands of a group of investigators makes it an unreliable clinical sign in the hands of a standard observer.

Frequently a spontaneous aching, and more frequently a "different feeling" in the sensory distribution of a nerve were early signs of sensory regeneration. Although many authors believe that pain produced by pressure upon a nerve distal to the point of injury has some prognostic significance, we did not find it so.

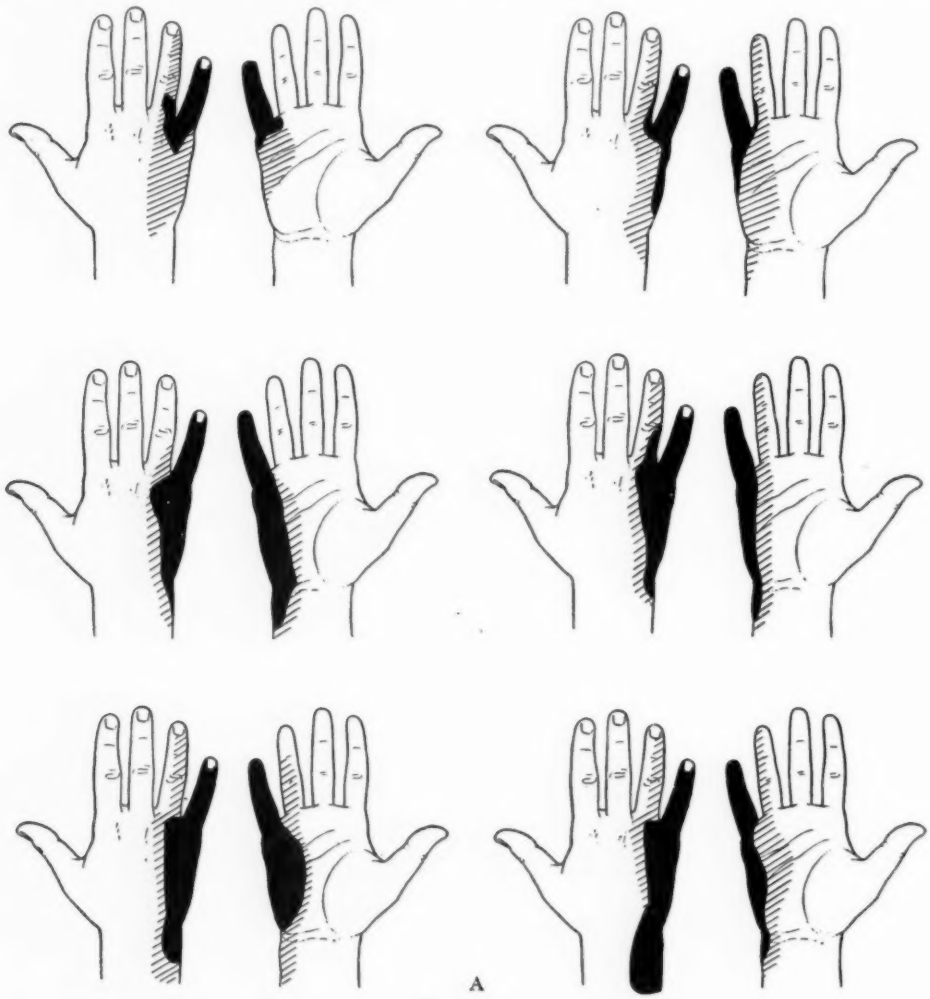
After the development of these early signs of regeneration sensation to objective stimulation returns, much as has been described by Head, although, as pointed out in the chapter on sensory Nerve Overlap, our interpretation of this return is materially different. We cannot emphasize too often that only when that portion of the area representing the anatomic sensory supply of an injured nerve which is removed from the influence of overlap, in other words *its isolated supply*, becomes sensitive can we say that regeneration is present. The recovery of sensation occurs in patches scattered over the previously anesthetic area and not only on its borders. It is notable that only once did sensation to pin prick and touch return in an area of isolated supply before there was a return of motor function.

Pattern of Sensory Recovery in Peripheral Nerve Lesions: A comparison of the sensory charts of complete lesions with those of recovering ones has brought out some interesting observations which merit description.

The return of sensibility to pain as the result of overlap in complete lesions follows a pattern so characteristic that it may be recognized at sight. For example, it never returns in the distal phalanges of the little finger in ulnar nerve lesions, nor in the distal phalanges of the index and middle fingers in median nerve lesions. It always occurs along the borders of an uninjured nerve and may well be described as a shrinkage (Fig. 64).

Contrasted with this, the pattern in recovering nerves is strikingly different. Although shrinkage occurs, other changes are always present. The material consisted of about 400 cases from which the general conclusions have been derived. From

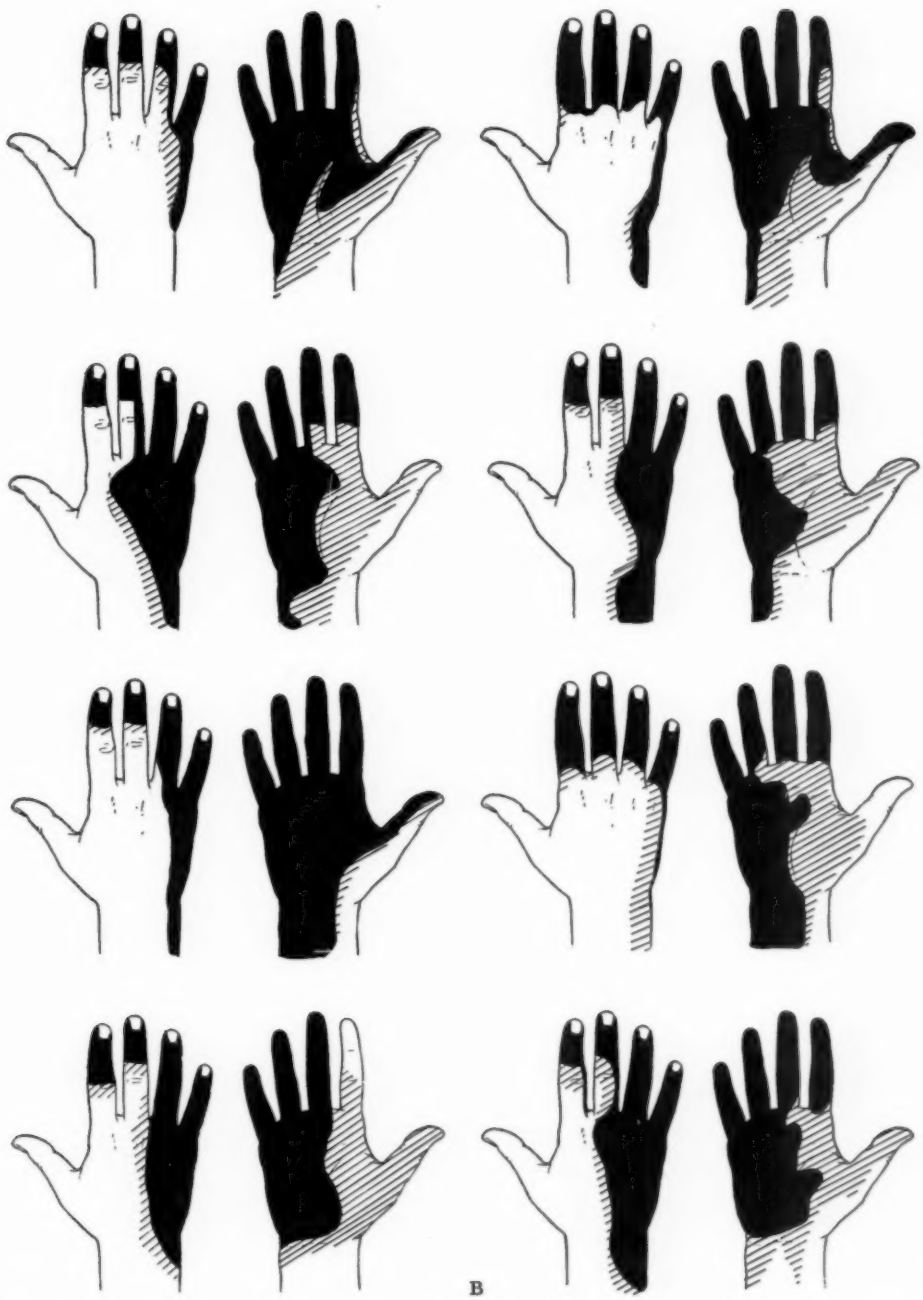
this material there have been selected a number of cases which recovered after operation, and these were contrasted with those cases which recovered spontaneously. No difference



A

FIG. 64.

could be detected between the cases which recovered following neurolysis or resection and suture, except in those in which prior to the neurolysis the sensory loss did not occupy completely the sensory cutaneous distribution of the nerve. In the latter, very early return of function in the partly anesthetic or analgesic area was found.



B

FIG. 64.

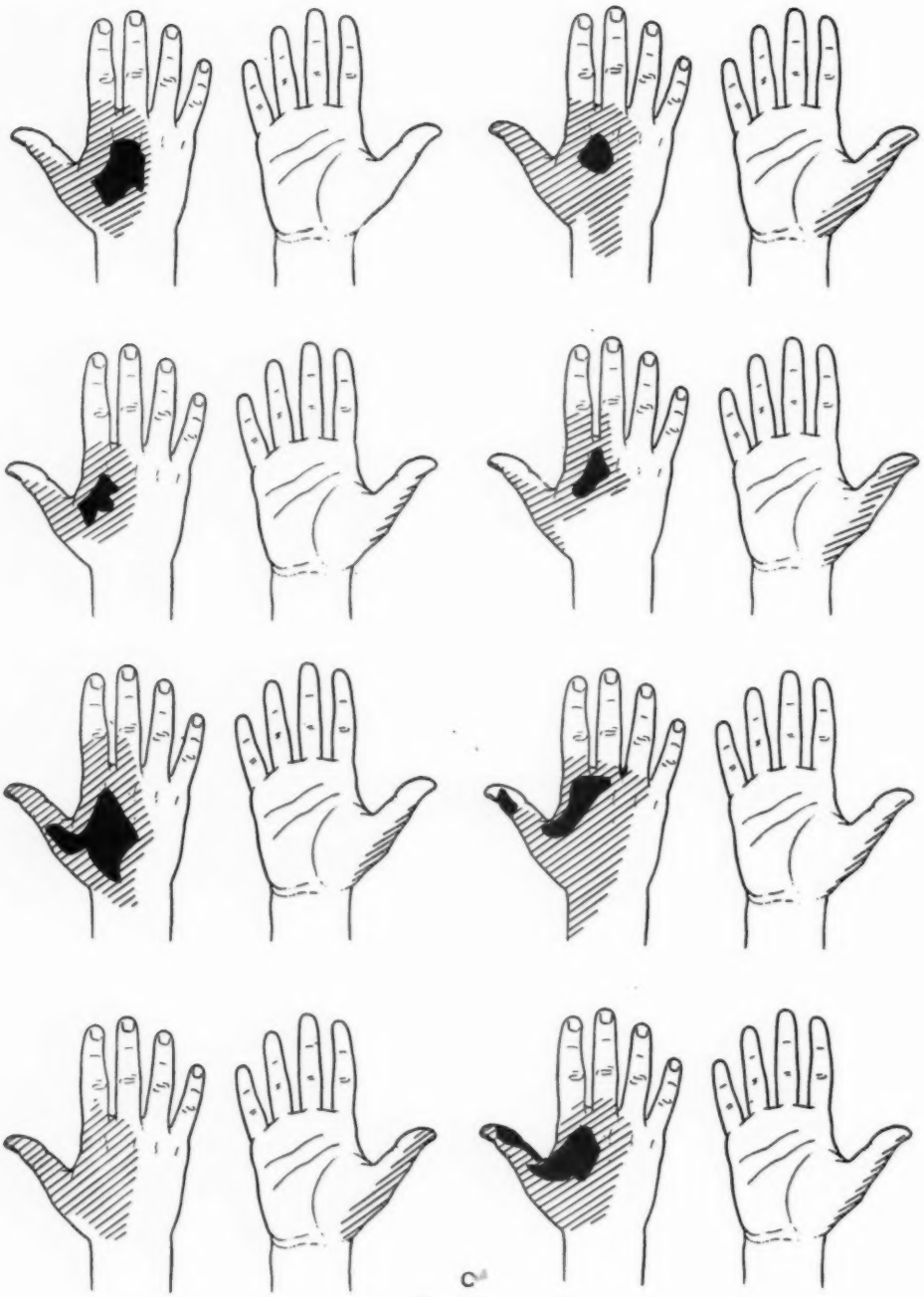


FIG. 64.

The characteristic features of the sensory loss of regenerating nerves may be enumerated as follows:

Return of sensibility to pain, touch or temperature sense

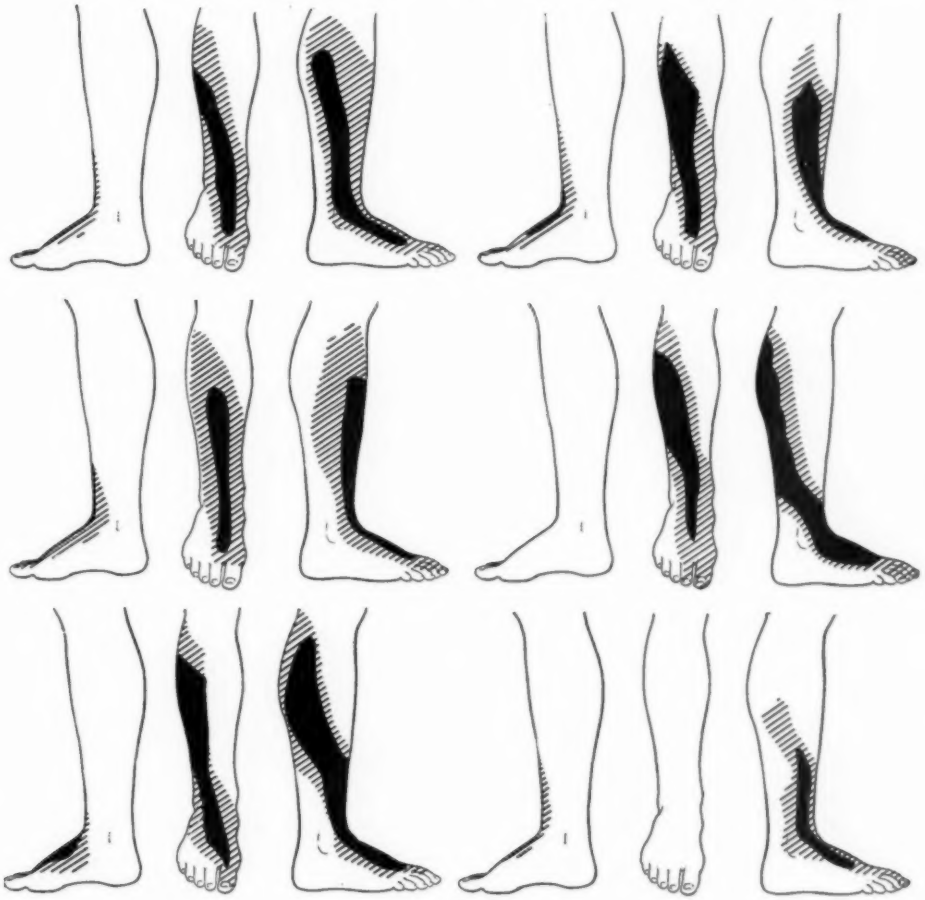


FIG. 64. Sensory loss in complete section of (A) ulnar nerve; (B) ulnar and median nerves; (C) radial nerve; (D) peroneal nerve. Note shrinkage due to nerve overlap.

in the isolated sensory supply of the injured nerve (Fig. 65).

Return of sensibility to pain, touch or temperature sense in patches some distance from the area supplied by an adjacent uninjured nerve (Fig. 66).

Return of sensibility to pain, touch or temperature sense in deep indentations (Fig. 67).

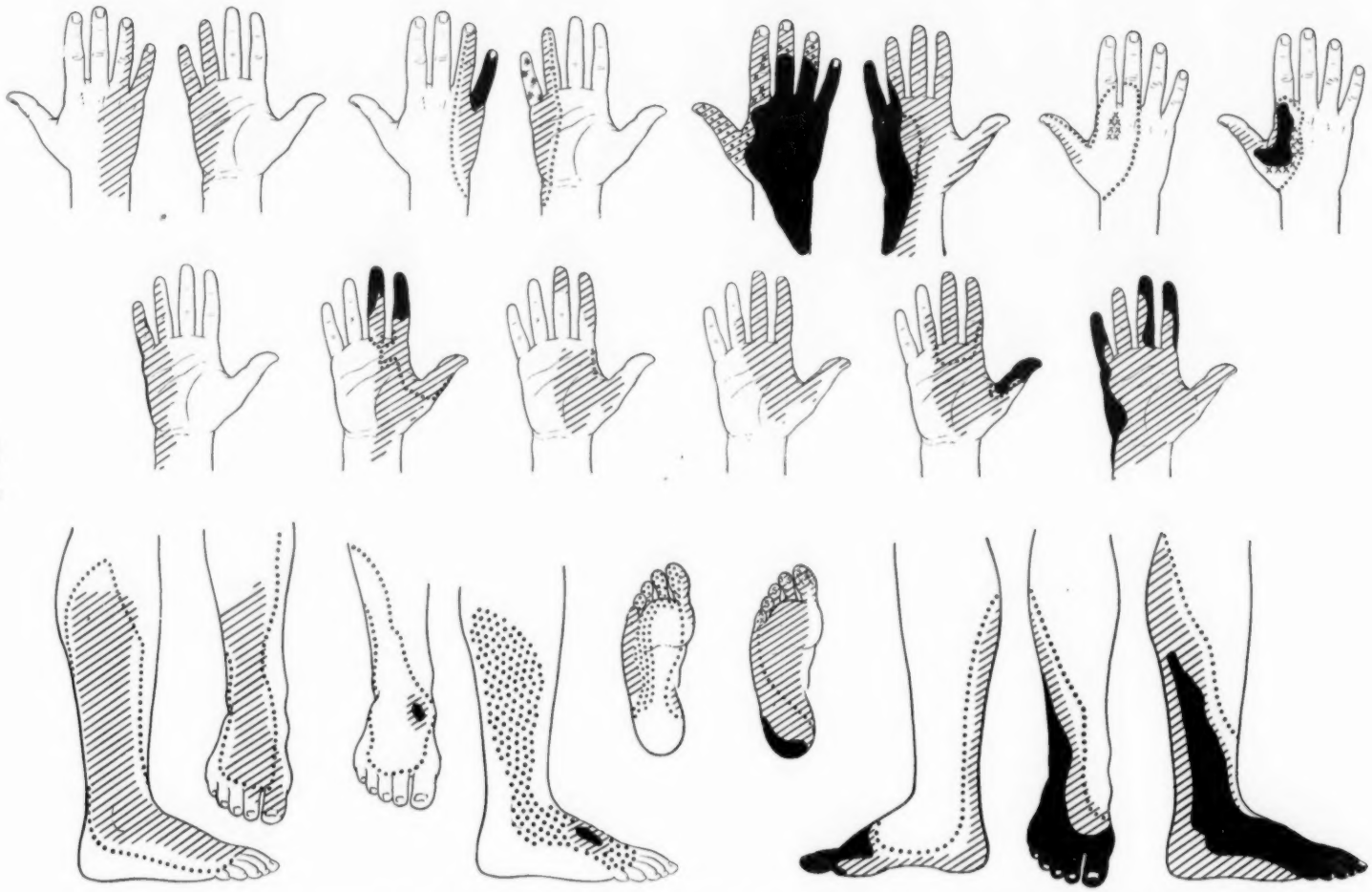


FIG. 65. Sensory loss in recovering lesions. Return of pain, touch or temperature sense in isolated supply of peripheral nerve.

Diminution of the degree of loss of sensation of pain, touch or temperature sense in the isolated sensory supply of a nerve (Fig. 68).

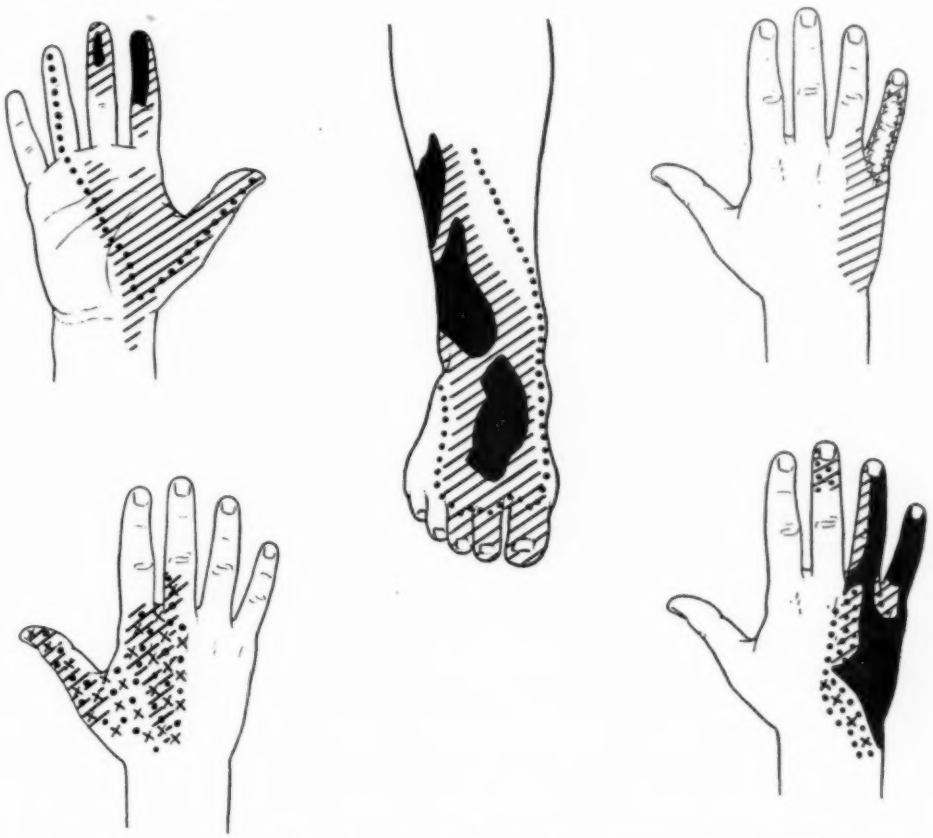


FIG. 66. Return of sensibility to pain, touch or temperature sense in patches some distance from area supplied by an adjacent nerve.

Return of sensation of pain, touch or temperature in the border between the sensory supply of two nerves simultaneously injured (Fig. 68).

Interlacing of the border of sensory loss of one type of sensation with that of another (Fig. 67).

ARREST OF MUSCLE ATROPHY AND RETURN OF TONICITY: These symptoms were not profitably employed in those cases which recovered some months after injury for reasons which have been already stated.

REACTION OF REGENERATION: It may be well to state that in the partial lesions which showed beginning recovery before the eighth month following injury, a response to faradism at

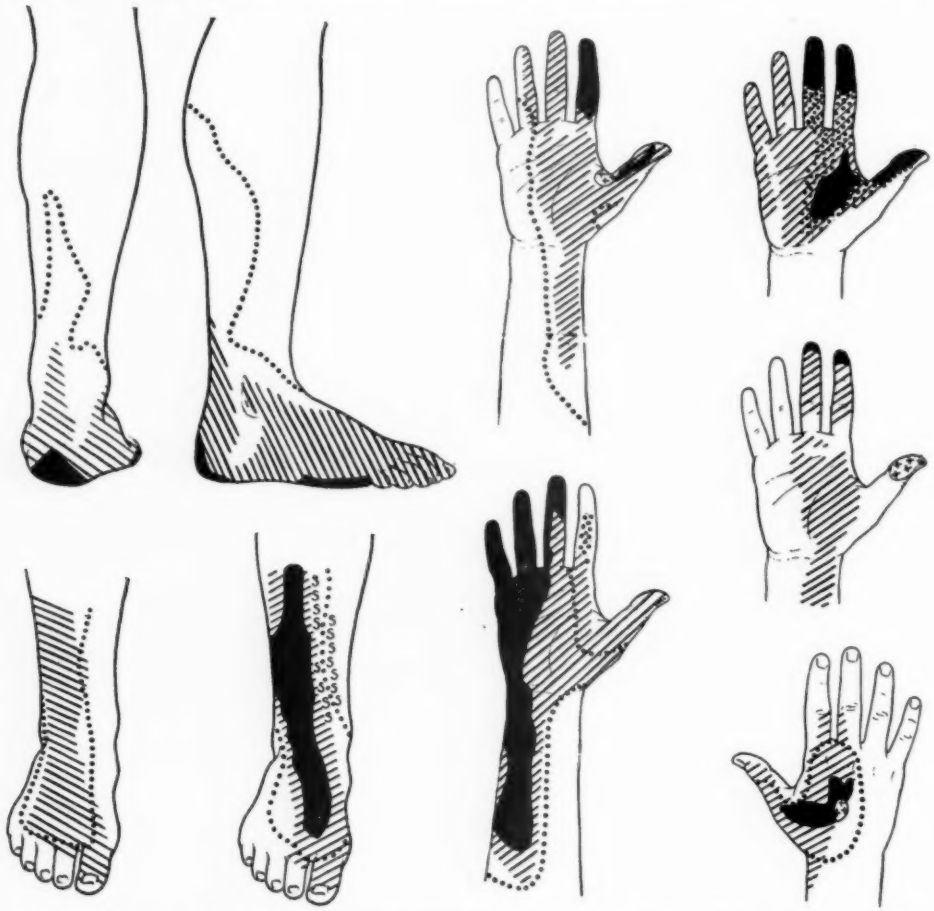


FIG. 67. Return of sensibility to pain, touch or temperature sense in deep indentations and interlacing patterns.

times returned before motion. At times motion was present and faradic response absent. The cases which showed beginning regeneration following resection and suture performed not less than six months following injury, never showed any return of response to faradism before the return of motion. The same is true of the cases which showed beginning spontaneous regeneration eight months or more after injury. In agree-

ment with Bénisty we found that faradic excitability of the nerve did not return before that of the muscle when percutaneous stimulation was used. The most reliable indication

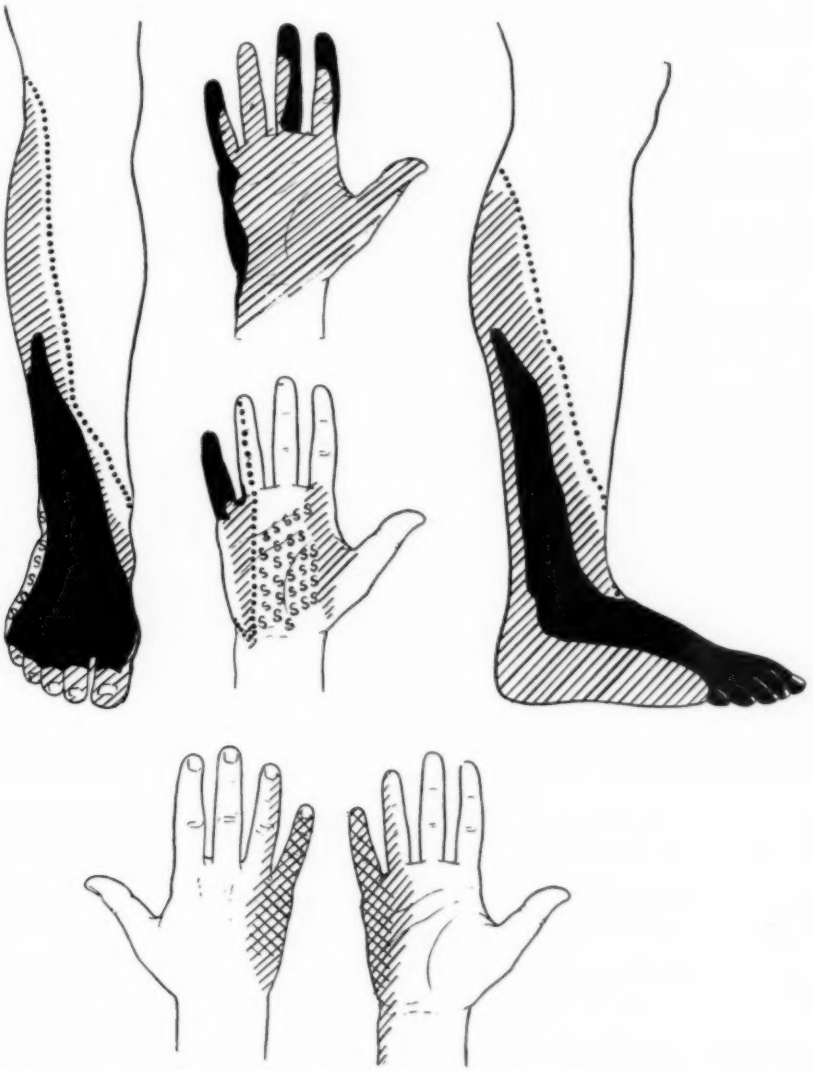


FIG. 68. Return of sensibility in zone between areas of two adjacent nerves and decrease in loss of pain in isolated supply area.

of recovery was an increase in the rapidity of the muscular contraction to the galvanic current.

Recovery of Voluntary Motion: In the interpretation of the significance of the return of motion relative to regeneration, proper recognition must be made of supplementary motility.

The order in which movement is restored to muscles paralyzed as the result of peripheral nerve lesions has a sufficient constancy so that a clinical individuality may be attributed to each nerve. Generally speaking, in severe lesions a certain degree of muscular tonicity returns before any reappearance of voluntary motion, but the methods of measurement are so inaccurate that this statement is the result of an impression and the finding cannot be used in a prognostic sense. At first voluntary movements are awkward and uncertain and frequently the reaction time of a movement is considerably lengthened. Attention must be directed to what has been called "an error in the switching" of the motor fibers which have not taken the proper direction and have not encountered each time the sheaths intended for their reception. For example, when a patient suffering from an injury to his radial nerve wishes to extend his wrist the supinator longus contracts powerfully and often in excess of the extensor carpi radialis muscle.

At times it has been noted that preceding the ability to produce voluntary motion the patient experiences a feeling of being able to produce that certain motion when he wills it. For example, in a radial nerve lesion before recovery has taken place, the patient may not have been able to sense the feeling of extension, whereas when recovery is taking place he begins to feel the sense of extending the wrist, although such extension may not be produced.

In our experience, the order of the return of function in severe lesions has been sensation to pinching over the isolated supply of a nerve, at times spontaneous aching in muscles, return of motion, return of other objective sensibility, and finally a return of electrical excitability. Following injury the length of time necessary to observe the first sign of return

of function in a complete physiologic interruption of a nerve is variable. The earliest critical return of sensory and motor function is commonly five months. In other cases it has occurred eighteen and twenty-four months after injury. Following primary sutures, recovery is demonstrable in eight to nine months. In late sutures and in severe spontaneously recovering lesions evidence of recovery may not be seen until the eighteenth month.

Chapter XIV

DEVELOPMENT AND STRUCTURE OF THE PERIPHERAL NERVOUS SYSTEM

The peripheral nervous system consists of groups of *nerve cells, ganglia,* bundles of myelinated and unmyelinated *nerve fibers* and specialized nerve endings. In addition to an anatomical difference the nerve fibers are physiologically dissimilar. *Afferent fibers* arise from cells of origin in the ganglionic crest outside the neural tube and carry sensory impulses from the periphery toward the spinal cord. The cells of origin of the *efferent fibers* are in the anterior horns of the grey matter of the spinal cord. These fibers carry motor impulses from the spinal cord to the periphery. Fibers of one or both types converge on each side of the spinal cord and form a *spinal nerve.* There is a pair of spinal nerves for each segment of the spinal cord.

The anlage of the entire nervous system is a thickened band of ectoderm, the *neural tube,* situated along the mid-dorsal line of the embryo. A groove is formed in this neural plate and later it is bounded laterally by paired *neural folds.* In turn these folds meet, fuse and form the neural tube from which all nervous tissue arises with but one exception. A longitudinal ridge of cells appears laterally where the neural plate and general ectoderm join. This is the *neural* or *ganglion crest.* Thus, when the neural tube closes and the general ectoderm separates from it the cells of the ganglion crest lie in a dorsolateral position to the neural tube. They later separate into right and left neural crests, distinct from the neural tube. Still later they take up a more ventral position and then this band of cells extends the entire length of the neural tube which now develops into the spinal cord. At regular intervals, or segments, of the spinal cord the neural crest cells proliferate, enlarge and form the *spinal ganglia.* (Fig. 69.)

The primitive *germinal cells* of the neural tube divide mitotically and form *ependymal* and *indifferent* cells. From the

indifferent cells *spongioblasts* and *neuroblasts* are formed. Spongioblasts develop into *neuroglia cells* and *fibers* and thus make up the supporting tissue of the spinal cord. The *neuro-*

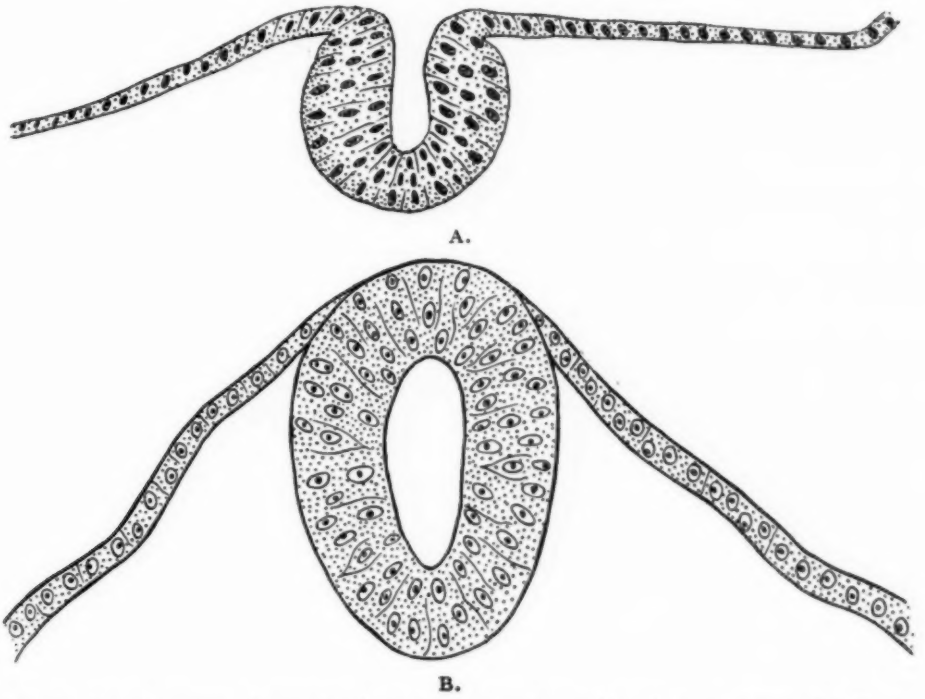


FIG. 69. Development of neural tube in human embryos (Arey); A, at 2 mm. (Mall); B, at 2.7 mm. (Kollmann).

blasts develop into nerve cells with an *axis cylinder* and *dendritic processes* and thus become *neurons*. The axis cylinders of the nerve cells in the anterior horns of the grey matter of the spinal cord emerge from the cord and form the *anterior roots* of the spinal nerves.

In a similar manner the cells of the spinal ganglia differentiate into *ganglion cells* and *supporting cells* comparable to the neuroblasts and spongioblasts of the spinal cord. The ganglion cells are pear-shaped and have a process at each pole. The process which is directed centrally enters the *posterior horn* of the grey matter of the spinal cord as the *dorsal root*. Within the spinal cord its collateral branches form a connection by

synapses with the dendritic processes of the nerve cells of the anterior horns. The peripheral processes of the ganglion cells join in a bundle and form the *posterior spinal roots*. As stated

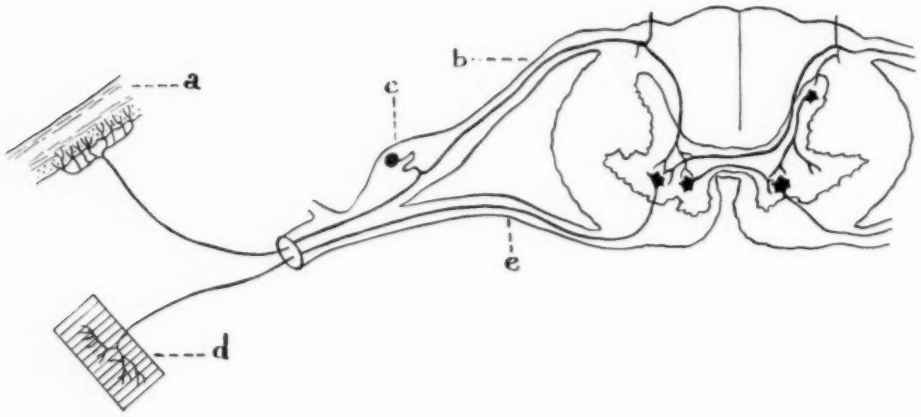


FIG. 70. Formation of a spinal nerve. *a*, Skin; *b*, Dorsal root; *c*, Spinal ganglion; *d*, Muscle; *e*, Ventral root.

before, the anterior and posterior spinal roots converge to form the trunk of the spinal nerve (Fig. 70).

NEURON DOCTRINE

The concept of the development of the spinal nerves given in the facts just presented has come to be known as the *neuron doctrine*. This doctrine assumes that the neuron is the structural unit of the nervous system and that axons and dendrites are outgrowths from nerve cells. Experimental evidence supports this hypothesis, originally advanced by His. Waller showed that if a nerve fiber is sectioned, that part distal to the point of section and separated from its cell of origin will degenerate. That part of the nerve fiber still attached to the cell will regenerate. Further evidence in support of this theory has been supplied by Harrison. He removed the ganglion crest from frog larvae and showed that no peripheral nerves developed. When the crest was transplanted to abnormal positions in the body of the embryo, it gave rise to nerves which followed paths where normally no nerves run.

A second theory (Hensen's hypothesis) assumes that protoplasmic connections remain between a chain of cells. Some of these connections persist and differentiate into nerve fibers while the others disappear. This theory has been supported by Schwann, Balfour and Bethe and has been modified by Apathy and Schulze and by Held. It has not been widely credited.

The foregoing may be summarized as follows: the axis cylinder of a nerve fiber is the outgrowth of a single cell. It remains attached to this cell throughout. It grows from the center toward the periphery and establishes connections with an end organ. If any part of it becomes separated from its cell of origin, that portion degenerates.

Histology

The supporting cells of the spinal ganglia at first form a syncytium which surrounds the ganglion cells but later they develop into flattened *capsule cells* which envelop the ganglion cells. They differentiate further into *sheath cells* and migrate peripherally with the nerve fibers of both posterior and anterior spinal roots. These sheath cells enclose bundles of fibers but soon proliferate and each nerve fiber becomes enclosed in a continuous sheath of cells. This is known as the *neurilemma* or sheath of Schwann. It is interrupted segmentally by constrictions known as the *nodes of Ranvier*, and each constriction represents the limits of one sheath cell. The neurilemma is extremely important in any consideration of the surgery of the nervous system. A neurilemma is not present about the fibers within the brain or spinal cord and section of the fibers in these locations is never followed by attempts at regeneration of the end still attached to the cell of origin. This is, of course, quite the opposite after section of the nerve fibers in peripheral nerves about which a neurilemma is present. Consequently it has been said that a neurilemma is necessary for regeneration after a lesion of the nervous system.

Within this outer covering, an inner *myelin* or *medullary sheath* develops about many but not all nerve fibers.[1] Hence, the division into *myelinated* and *non-myelinated* fibers, both of which have a neurilemma in a peripheral nerve. The myelin sheath is a spongy framework of *neurokeratin* in the interstices of which is myelin, a mixture of fats and lipoids. This substance plays an important part in the microscopic picture presented by a degenerating nerve fiber. The myelinated fibers have a glistening white appearance. This gives the characteristic appearance to the peripheral nerves. Non-myelinated fibers are present in abundance in peripheral nerves, however. It should not be forgotten that the myelin sheath and the neurilemma sheath are distinct structures and that both myelinated and non-myelinated fibers may have a neurilemma. Individual myelinated or non-myelinated nerve fibers may vary considerably in diameter. Their physiological function cannot be determined from their microscopic appearance. The proportion between myelinated and non-myelinated fibers within a peripheral nerve also varies considerably and as yet no relation between function and this proportion is clear.

Within a peripheral nerve the myelinated and non-myelinated nerve fibers are gathered together in bundles which vary in number, size and arrangement and give to each individual nerve a characteristic *internal topography*. The loose tissue which surrounds each entire nerve is the *epineurium* (Fig. 71). It consists of longitudinal bundles of connective tissue associated with elastic fibers and fat cells. It contains the nutrient blood vessels which supply the nerve. Each bundle of nerve fibers within the nerve is surrounded by a lamellar layer of connective tissue, whose flattened cells lie in contact so they form an almost continuous membrane. This is the *perineurium*. In the larger peripheral nerves prolongations of the perineurium extend into the nerve bundle between the

[1] The origin of myelin is in doubt. Ranvier believed it to be derived from the neurilemma. Kölliker regarded it as a product of the axis cylinder. Bardeen believes it to be an intercellular substance precipitated by the influence of the axis cylinder.

individual nerve fibers. These septa are known as the *endoneurium*.

Bardeleben's conception that although nerves are made up of

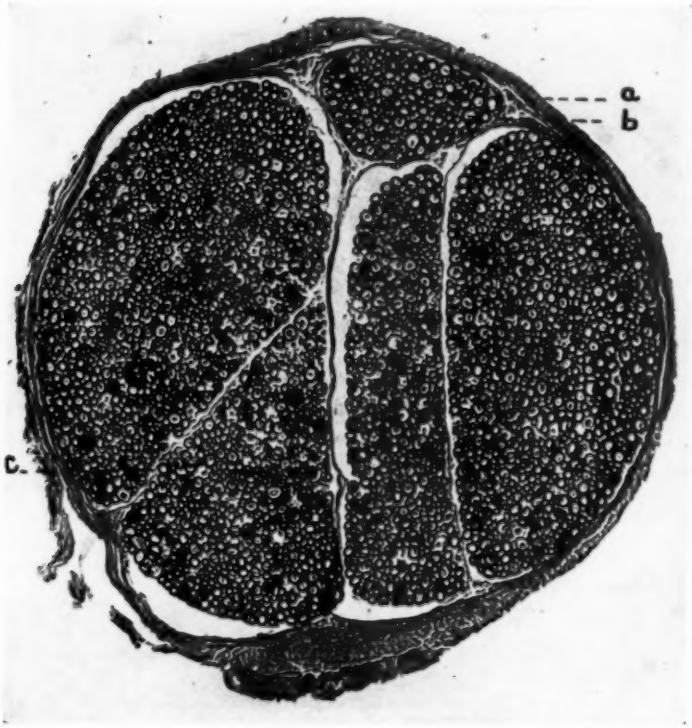


FIG. 71. Microscopic appearance of cross section of normal peripheral nerve. *a*, Epineurium; *b*, Perineurium; *c*, Endoneurium.

anastomosing bundles of fibers, the actual course of the fibers is a straight one from the plexus to the point of origin of a peripheral branch, was studied again in the material collected during the World War. Independently, in 1910, Stoeffel stated that the arrangement of the bundles, or *funiculi*, of nerve fibers within a peripheral nerve trunk were constant for that nerve at any given level. Thus, certain muscles or sensory areas innervated by a particular peripheral nerve are served by a funiculus of nerve fibers which occupies a definite circumferential position within the nerve at a given level. This view would indicate a very accurate funicular anatomy and the recognition

and observance of these anatomical facts would play an important rôle in the suture of divided nerve ends. Any disarrangement of the funiculi, such as the apposition of ends of sensory

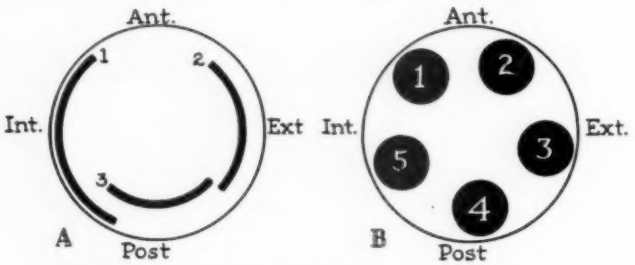


FIG. 72. Funicular topography of radial nerve.

A. (After Kraus and Ingham.) 1, Triceps; 2, Brachioradialis; 3, Extensor carpi radialis.

B. (After Stoeffel.) 1, Ramus superficialis; 2, Brachioradialis; 3, Extensors of the wrist; 4, Ramus profundus; 5, Supinator.

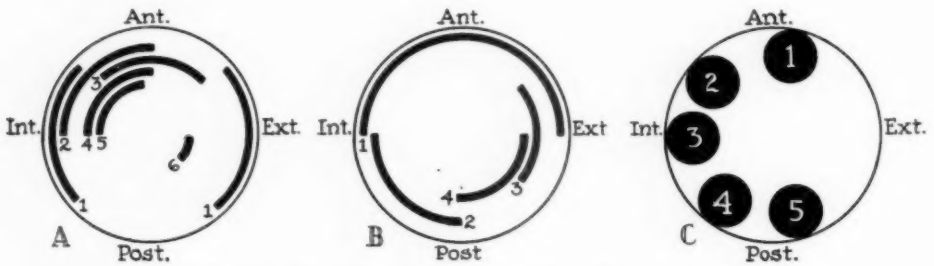


FIG. 73. Funicular topography of median nerve.

A. (After Kraus and Ingham) (Midarm level). 1, Pronator radii teres; 2, Flexor carpi radialis; 3, Palmaris longus; 4, Flexores digitorum; 5, Flexor pollicis; 6, Pronator quadratus.

B. (After Kraus and Ingham) (Midforearm level). 1, Sensory; 2, Opponens pollicis; 3, Abductor pollicis; 4, Lumbricales.

C. (After Stoeffel) (Arm level). 1, Palmaris longus, flexor carpi radialis and pronator teres; 2, Thenar muscles; 3, 4, Flexor digitorum sublimis; 5, Flexor digitorum profundus.

to motor fibers would impair the results of the surgical repair of nerve lesions. (Fig. 72.)

Marie, Gosset and Meige, Kraus and Ingham, and Putti have strengthened the view advocated by Stoeffel (Fig. 73). All of the experiments carried out by these men have been by the method of bipolar stimulation on the surface of nerve trunks exposed upon operation. Several serious objections to the results obtained from such experiments immediately

suggest themselves. (Fig. 74.) It would be difficult to obtain the same level on a given nerve for stimulation in different individuals. As a matter of fact, there have been shown to be marked

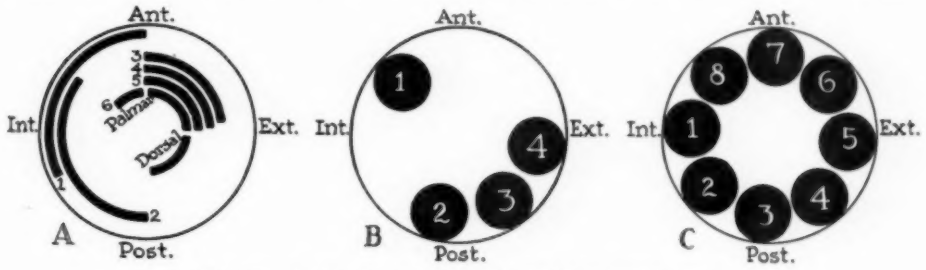


FIG. 74. Funicular topography of the ulnar nerve.

A. (After Kraus and Ingham). 1. Flexor carpi ulnaris; 2, Flexor profundus digitorum; 3, Hypothenar muscles; 4, Interossei; 5, Adductor pollicis; 6, Sensory.

B. (After Stoeffel) (Level of midarm). 1. Sensory fibers; 2, Flexor carpi ulnaris; 3, Flexor digitorum profundus; 4, Ramus profundus.

C. (After Stoeffel) (Level of midforearm). 1. Dorsal ramus to hand; 2, Ramus profundus; 3, Hypothenar muscles; 4, Interossei and lumbricales; 5, Adductor pollicis; 6, Deep head of flexor pollicis brevis; 7, Sensory fibers; 8, Ramus superficialis.

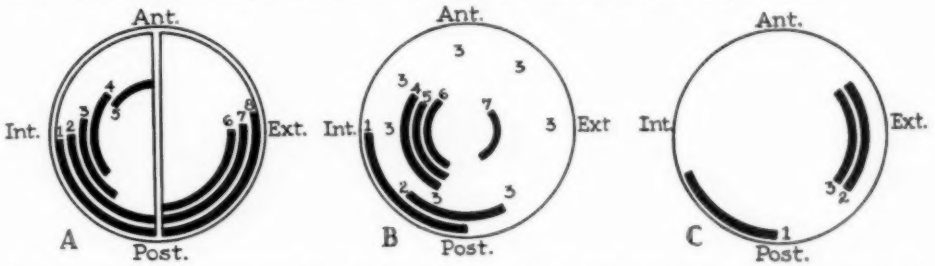


FIG. 75. Funicular topography of (A) sciatic nerve (after Kraus and Ingham); (B) tibial nerve, and (C) peroneal nerve.

A. 1, Hamstrings; 2, Gastrocnemius and soleus; 3, Flexor hallucis longus; 4, Flexor digitorum longus; 5, Tibialis posticus; 6, Peronei; 7, Tibialis anticus; 8, Extensors of toes.

B. 1, Hamstrings; 2, Gastrocnemius; 3, Tibialis posticus; 4, Flexor digitorum longus; 5, Flexor hallucis longus; 6, Intrinsic; 7, Flexor hallucis brevis.

C. 1, Peronei; 2, Tibialis anticus; 3, Extensors of toes.

variations in the same nerve on the opposite side in the same individual. The funiculi are so closely related to one another that the results of electrical stimulation upon the surface of the nerve would be difficult to attribute to a given funiculus in a definite quadrant. Finally, from a practical surgical standpoint, the recognition of the funicular topography by stimulation of the cross-section surface of a divided

nerve would be useless because of the degeneration in the distal fragment. The recognition of funicular topography in a peripheral nerve is only accurate for a given nerve at a particular level and at a definite time. Innumerable mechanical factors make impossible the stimulation of the same point at the same level on a nerve at different times. (Fig. 75.)

The acceptance of this theory would have a serious effect upon the future of the surgery of peripheral nerves. It has been denied vigorously by Heinemann, Borchardt and Wjasmenski, Langley and Hashimoto, Compton, Dustin, and McKinley. All of these investigators found the existence of innumerable internal plexuses within the peripheral nerves by which interfunicular connections are made. They also found that even at levels taken at intervals of 3 cm., the cross-section appearance of the nerve trunk was so different as to make identification of definite funiculi hopeless. None of these workers found that the funiculi constantly ran a separate and distinct course for any great distance.

While all of the facts brought out by the individuals who have investigated this matter are not in agreement in each case, nevertheless there are some unquestionable conclusions which should be borne in mind as far as possible in the surgical treatment of nerve injuries.

In the *radial* nerve there are two fasciculi which are quite definite. The fibers for the supinator longus occupy the external border of the middle third of the arm. The fibers for the extensor communis digitorum are placed upon the posterointernal surface of the nerve in the same area.

In the *median* nerve during its course in the arm, the fibers for the pronator muscles lie on the external border of the nerve while those for the flexor sublimis digitorum occupy the internal border. According to Stoeffel, fibers for the thenar muscles are intermingled with the sensory fasciculus. This group of fibers occupies three-fifths of the nerve trunk.

Intraneural localization within the *ulnar* nerve is more uncertain than in any of the larger mixed nerve trunks. Bénisty

states, however, that the fibers for the interossei muscles and the sensory fibers occupy the internal border of the nerve. The fibers for the deep flexors of the fourth and fifth fingers are located on the external border.

Only one group of fibers appears to be localizable in the *peroneal* nerve and that is the fibers for the tibialis anticus on the anteromedial side of the nerve.

In the *tibial nerve*, the posterior surface of the nerve is occupied by fibers which go to the gastrocnemius and soleus muscles. The fibers for the flexor longus hallucis are situated on the external border while those for the tibialis posticus are located on the anterior surface of the nerve.

Nerve Endings

The nerve fibers which grow out from the anterior horn cells of the spinal cord and from the spinal ganglion cells have characteristic terminations which are known as *motor* and *sensory* nerve endings. Motor nerve endings terminate in smooth, cardiac and striated muscle and here we are concerned only with the latter. Sensory endings may be classified as:

1. Free endings.
2. Muscle spindles.
3. Tendon spindles.
4. Terminal corpuscles:
   (a) Tactile.
   (b) Genital.
   (c) Bulbous.
   (d) Articular.
   (e) Cylindrical.
   (f) Lamellar.

Motor Endings: Neuraxons of the anterior roots form plexuses of medullated fibers in the perimysium of striated muscle fibers from which they extend into the muscle fasciculi. Each muscle fiber receives one and sometimes two of these branches. The connective tissue sheath of the nerve fiber blends with the perimysium and the neurilemma is continuous

with the sarcolemma. On the inner side of the sarcolemma the myelin sheath ends abruptly and the nerve fiber ramifies in a granular mass, which is probably modified sarcoplasm and

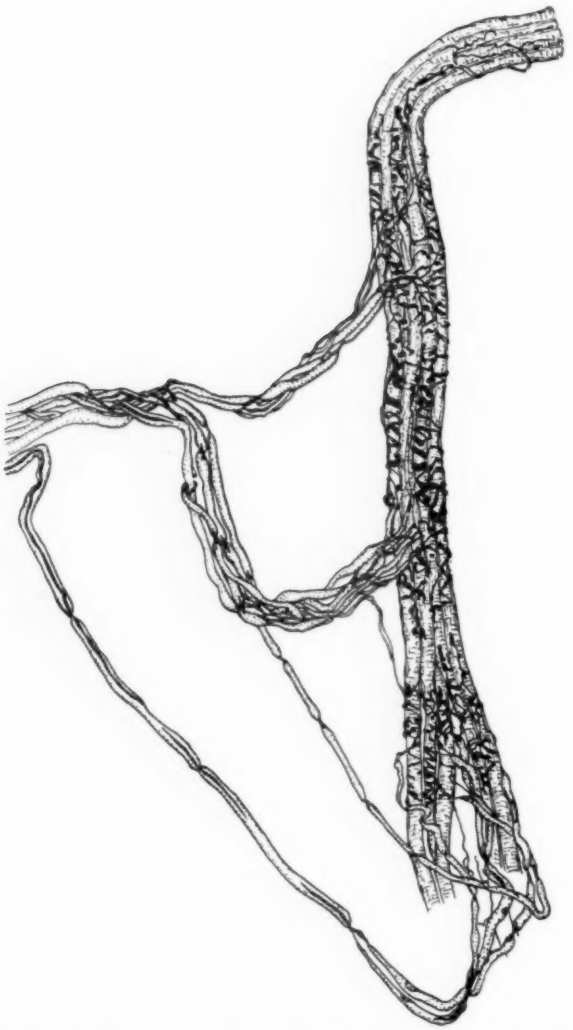


FIG. 76. Neuromuscular nerve end-organ from a dog. The figure shows the intrafusal muscle-fibers, the nerve fibers and their terminations, but not the capsule nor the sheath of Henle. Methylene-blue stain. (Huber and DeWitt.) (Ranson.)

which may contain muscle nuclei. This structure forms a distinct elevation which has received the name of a *motor end plate* (Fig. 76). Smaller non-myelinated fibers, independent of

the larger myelinated fibers, end in rings, loops or nets either within the sarcoplasm of a typical motor end plate, or as small independent end plates (Fig. 77).

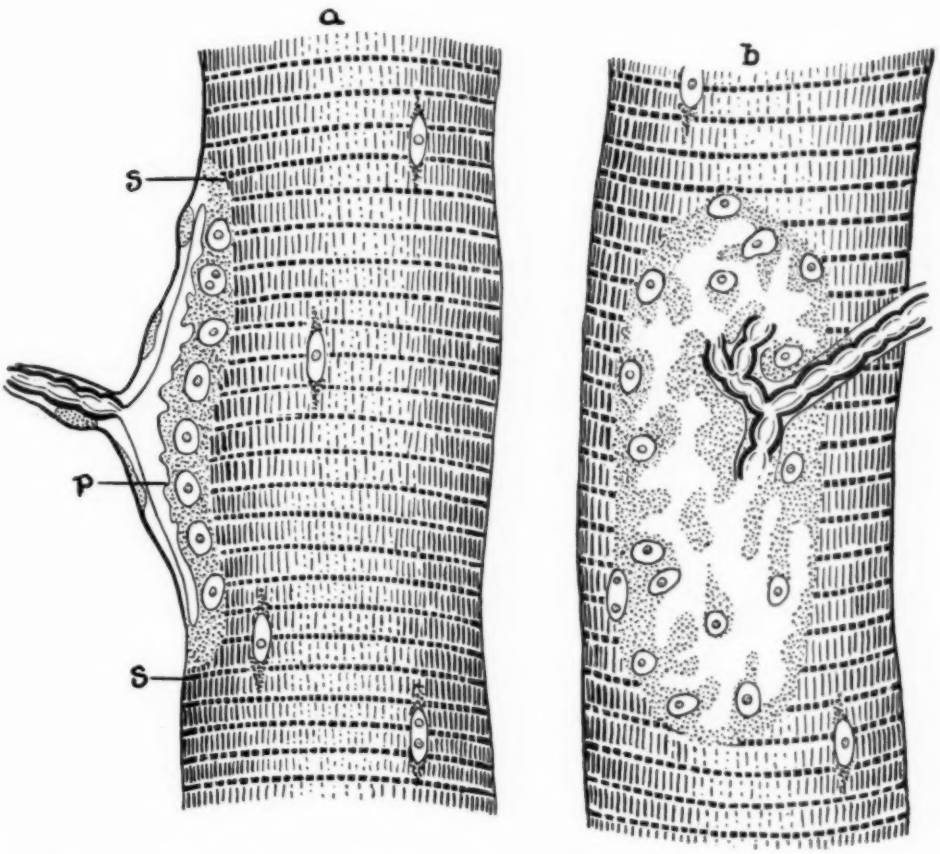


FIG. 77. Nerve ending in muscular fiber of a lizard. *a*, End organ seen in profile; *b*, from surface. *s*, Sarcolemma; *p*, Expansion of axis cylinder. Beneath this is granular protoplasm containing a number of large clear nuclei and constituting the "sole" of the end organ. In *b* expansion of axis cylinder appears as a clear network, branching from divisions of medullated fiber. (Kühne in Quain's Anatomy.) (Ranson.)

SENSORY ENDINGS: Free endings of sensory fibers to the epidermis and to the corneal and oral epithelia penetrate the basal layer and pass between the cells as unsheathed fibers. The extremities of the fibers are pointed or club shaped. They come in contact with epithelial cells but do not enter them. These

endings occur not only in stratified epithelia but also in muscle, tendon and connective tissue (Fig. 78).

Muscle spindles are slender groups of muscle fibers around

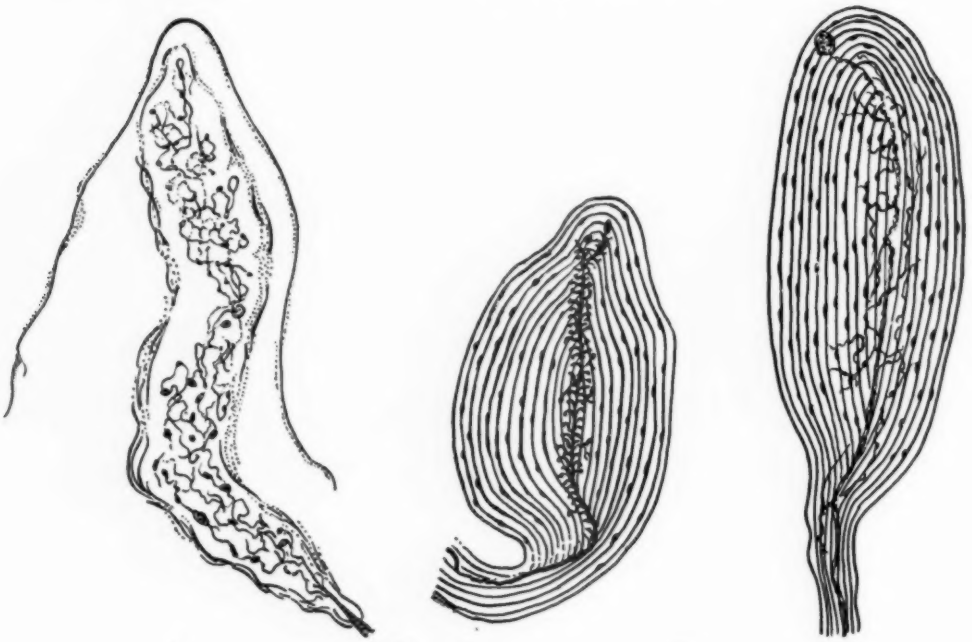


FIG. 78.

which nerve fibers terminate. The spindles are surrounded by a thick connective tissue capsule continuous with the perimysium. Three or four nerve fibers terminate in each spindle and their connective tissue sheaths blend with the perimysium. These fibers lose their myelin as they pass into the muscle cells. They may encircle the muscle fibers of the spindle to form spirals or rings.

Tendon spindles are small portions of the tendon enclosed in sheaths of connective tissue. The few nerve fibers which terminate in tendon spindles lose their sheaths, branch freely and end in club-shaped enlargements.

Terminal corpuscles are nerve endings which consist of a coarse nerve fiber surrounded by a semifluid intercellular substance and enclosed in a connective tissue capsule. *Tactile* corpuscles are elliptical in shape and contain several myelinated

fibers which enter the lower end of the corpuscle and immediately lose their myelin sheaths. They have a spiral course through the corpuscle. Tactile corpuscles are found in connec-

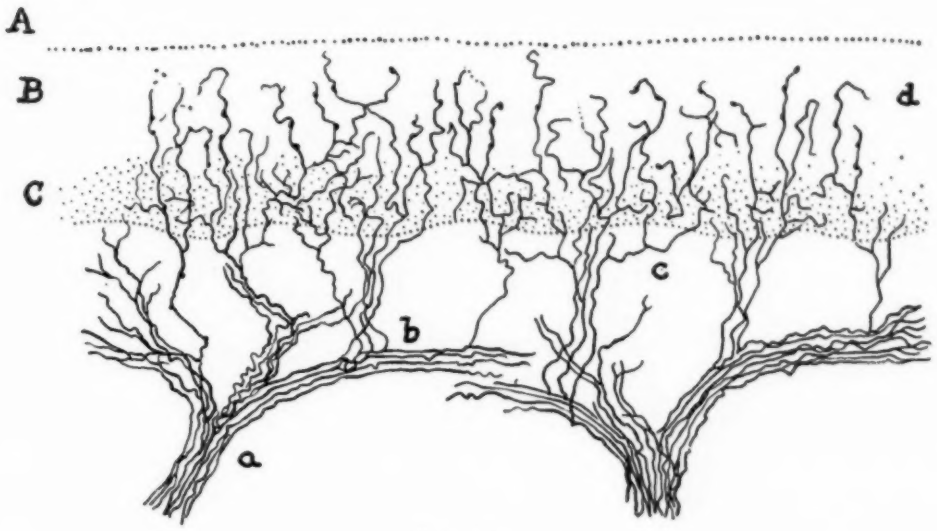


FIG. 78c.

FIG. 78. Types of sensory nerve endings.

A. Meissner's tactile corpuscle. Methylene-blue stain. (Dogiel, Böhn-Davidoff-Huber.) (Ranson.)

B. Pacinian corpuscles from mesorectum of kitten. *a*, Fine branches of central fiber; *b*, network of fine nerve fibers about central fiber. Methylene-blue stain. (Sala, Böhm-Davidoff-Huber.) (Ranson.)

C. Free nerve endings in epidermis of cat's paw. A, Stratum corneum; B, Stratum germinativum Malpighii and C, Its deepest portion. *a*, Large nerve trunk; *b*, Collateral fibers; *c*, Terminal branches; *d*, Terminations among epithelial cells. Golgi method. (Cajal.) (Ranson.)

tive tissue elevations just beneath the epidermis of the soles, palms and finger tips. *Genital* corpuscles are large round bodies which receive as many as ten nerve fibers. They are deeply placed beneath the epithelium of the glans penis, clitoris and adjoining tissues. *Bulbous* corpuscles are smaller, round or oval bodies with thin capsules and fewer fibers. They are found in the superficial connective tissue of the glans penis and clitoris. *Articular* corpuscles are found near the joints and are

similar in structure to the bulbous corpuscles. *Cylindrical* corpuscles contain a single nerve fiber, with few or no branches, which terminates in a rounded extremity. The fiber is surrounded by a semifluid substance which is enclosed in a few concentric layers of cells continuous with the sheath of the nerve. They are found in the mucus membrane of the mouth and in the connective tissue of muscles and tendons. *Lamellar* corpuscles are elliptical in shape. The axial core of the corpuscle is surrounded by concentric layers of a perineurium distended with fluid. A single large nerve fiber enters one end of the corpuscle and loses its myelin sheath. As it extends through the lamellae without branching it may become flattened and band-like or may divide at its terminal end and form a coil of branches. These corpuscles are found in the subcutaneous tissues of the hand and foot, near joints, in the periosteum, and in the connective tissue about large blood vessels and nerves and in tendon sheaths.

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